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THE PROJECTION OF THE OLFACTORY EPITHELIUM ON THE OLFACTORY BULB IN THE RABBIT

BY

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From the Department of Anatomy, University of Oxford

In a previous study (Le Gros Clark and Warwick, 1946) the degeneration of olfactory receptors in the rabbit following complete or partial ablation of the olfactory bulb was examined by reference to sections of the mucosa covering the septal cartilage, stained by Bodian's protargol method. Evidence was advanced to show that this is a true secondary degeneration following interruption of the primary olfactory neurons, and not the result of other factors such as vascular disturbance. It was found that the degeneration of the olfactory receptors occurs with great rapidity, for they undergo almost complete disintegration one week after removal of the bulb. The atrophy of the receptors is associated with a shrinkage in depth of the whole epithelium. The histological picture of the septal epithelium following partial lesions of the bulb incidentally led to the conclusion that there is no definite localized projection of different areas of the olfactory epithelium on to the bulb, for such lesions appeared to lead to a general thinning out of the receptors rather than to localized areas of complete degeneration. Later, evidence was brought forward by Adrian (1950), on the basis of electrophysiological studies, that there is in fact some degree of localized projection, though of a rather diffuse kind. He further made the interesting suggestion that this may have some importance as a basis for olfactory discrimination. It therefore appeared desirable to investigate the problem further by experimental anatomical methods, without limiting observations to a restricted area of the septal mucosa. As will be seen, this more extended enquiry has provided definite evidence of a general type of localization in the projection of the olfactory epithelium on the olfactory bulb.

Material and Methods

Partial or complete ablations of the bulb were made in 14 rabbits. Young animals, about 3 months old, were used for the experiments in order to eliminate as far as possible the complications of chronic rhinitis which is liable to affect older laboratory animals. Under nembutal anaesthesia, and with aseptic precautions, the bulb was exposed on one side by removing the frontal bone covering it. The lesions were effected with a fine-bladed scalpel, and in every case the resulting haemorrhage was readily controlled by slight pressure with a pledget of wool. The animals were allowed to survive two to six weeks. The brain and olfactory mucosa were fixed by perfusion through the aorta of 5% formol saline. The frontal poles of the brain, with the attached remnants of the operated bulb and the normal bulb of the opposite side, were removed, embedded in one block, and cut in serial sections. The latter were stained with haematoxylin and eosin or methylene blue. The whole of that part of the nasal cavity containing the olfactory epithelium was resected and, after decalcification in 5% nitric acid, serially sectioned. Every fiftieth section was mounted and stained with haematoxylin and eosin.

From the serial sections of the olfactory bulbs the position and extent of the lesion in each experiment were defined. For several reasons, however, this could only be done approximately. In the first place, the operation usually resulted in some distortion of the olfactory bulb (with considerable dilatation of the olfactory ventricle), so that it was not always easy to compare precisely the situation of the destroyed glomeruli with those of the normal bulb of the opposite side. Secondly, the zone of complete destruction was in many cases bordered by glomeruli which, though not directly affected by the lesion, had undergone varying degrees of atrophy consequent on the interruption of their afferent olfactory connexions. The assessment of the extent of this indirect, partial involvement of glomeruli was difficult. Account had also to be taken of secondary involvement due to vascular interruption, and as a result of this factor it was found that lesions which were intended to be small and localized had extended some way beyond the actual site of operation. For this reason, also, in three cases in which relatively large lesions had been made (with the intention of leaving intact small remnants of the glomerular system), it was found that total destruction of the bulb had in fact resulted.

The serial sections of the nasal cavity were used to plot the distribution of the secondary degeneration in the olfactory epithelium. The sections were stained

with haematoxylin and eosin because of the difficulty of obtaining in decalcified material a satisfactory and consistent demonstration of the olfactory receptors by methods of silver impregnation. The extent of the secondary degeneration was therefore determined indirectly by the degree of reduction in the total depth of the epithelial layer, which (as already noted) accompanies the atrophy and disintegration of the olfactory sensory cells. It is important to note, however, that this criterion of the extent of the retrograde degeneration of the receptors only provides data of an approximate kind, for besides the olfactory sensory elements the epithelium also contains supporting cells and basal cells, which do not themselves undergo degeneration. Further, in those areas, as in the recesses at the attachment of the turbinate processes, where the olfactory epithelium is thinner than elsewhere, and the proportion of supporting and basal cells to olfactory receptors somewhat greater, the reduction in the total depth of the epithelium in relation to the bulbar lesions tends to be correspondingly less. Lastly, with the histological methods employed, it is, of course, not possible to affirm that in areas where the olfactory epithelium appears normal a few scattered receptors may not have undergone atrophy, nor is it possible to state that in areas of severe degeneration scattered receptors may not have survived.

The degree of shrinkage of the epithelium was measured with an ocular micrometer over different parts of the septum and all the turbinate processes, and compared with the normal epithelium at corresponding points in the opposite side of the nasal cavity. In each local region compared, the mean of ten separate measurements was taken. In order to obtain a general indication of the distribution of degeneration of different degrees of severity (complete or almost complete, and partial or slight), two arbitrary grades were selected : (1) severe degeneration, in which the total depth of the epithelium had been reduced by at least 25% when compared with the normal side, and (2) moderate degeneration, in which the reduction was at least 10% (Fig. 1). Following total resection of one olfactory bulb, the average reduction in depth of the olfactory epithelium of that side in all areas (as measured on the sections) is 40%. In the first experiments, the animals were allowed to survive six weeks after operation in order to ensure that the maximum resulting degeneration of the olfactory epithelium had occurred. It was subsequently found that, in fact, this occurs by the end of two weeks. This is shown by the following comparisons of the percentage reduction in the depth of the olfactory epithelium in different regions after total ablation of the olfactory bulb in two cases in which the animals were killed two weeks and six weeks respectively after operation :—

Region	Experiment L.2 (2 weeks)	Experiment R.643 (6 weeks)
Septum	44	43
Nasoturbinal ..	45	45
Endoturbinal 1 ..	42	49
,, 2 ..	27	38
,, 3 ..	38	36
,, 4 ..	30	30
Ectoturbinal 1 ..	50	47
,, 2 ..	46	30
,, 3 ..	38	39

In three experiments with partial lesions of the olfactory bulb the results had to be discarded, because the sections of the nasal cavity showed evidence of rhinitis which made it impossible to define the areas of secondary degeneration of the olfactory epithelium with accuracy.

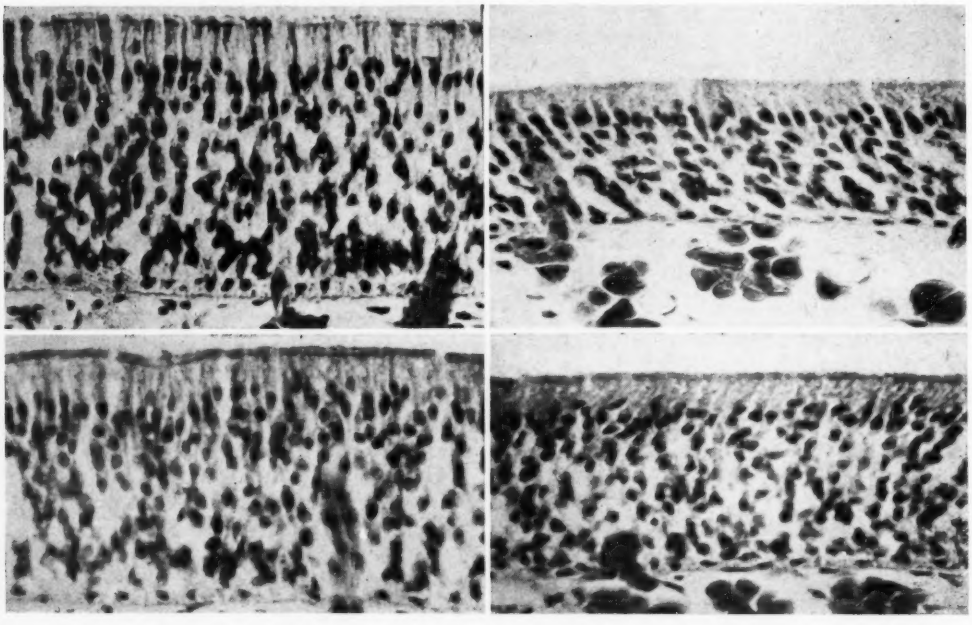

FIG. 1.—Sections of the olfactory epithelium from experiment R.146. Above is shown the epithelium over the nasoturbinal of the normal side (*a*) compared with that of the operated side (*b*). The latter illustrates a "severe degree" of secondary degeneration. Below is shown a part of the septal epithelium of the normal side (*c*) and the corresponding region of the operated side (*d*), illustrating a "moderate degree" of degeneration. (× 370.)

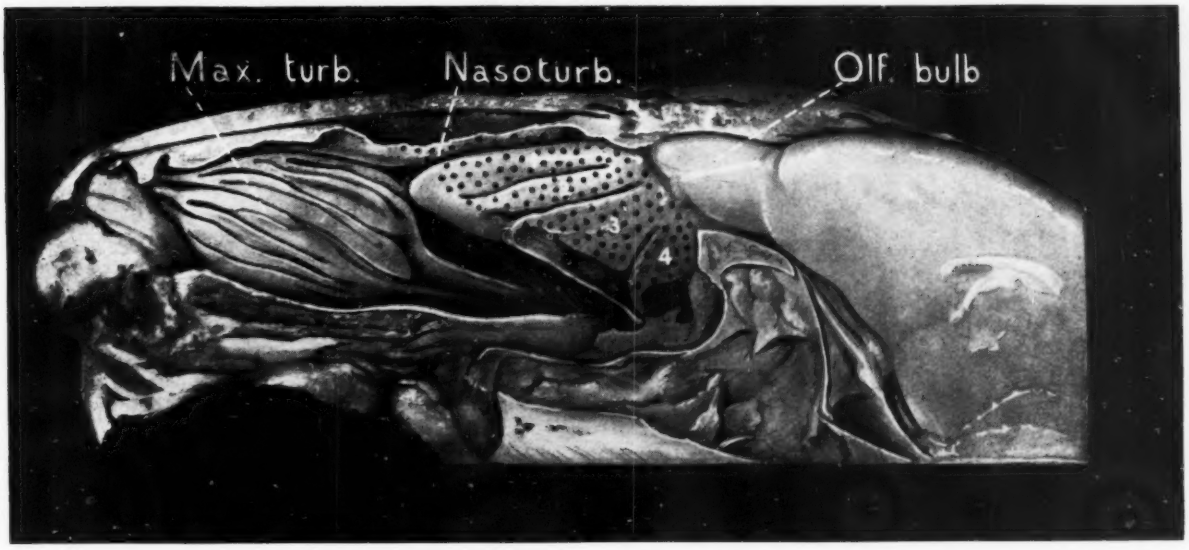

FIG. 2.—Sagittal section of a rabbit's head showing the appearance of the right nasal cavity after removal of the septum. The extent of the olfactory epithelium is indicated by the dotted area. The endoturbinals are numbered 1–4.

General Topography of the Olfactory Epithelium in the Rabbit

Before recording the results of individual experiments it is desirable to make a brief reference to the topography of the areas of olfactory epithelium in the rabbit. As is well known, in lower mammals this epithelium covers the postero-superior part of the septum and a complicated series of turbinate processes in the lateral part of the nasal cavity. In the rabbit (Fig. 2) there are four endoturbinals (processes of the ethmoid bone) whose free surfaces are apposed to the septum. Above the first (uppermost) endoturbinal is the nasoturbinal which extends forwards on the under surface of the nasal bone. In the roof of the nasal cavity, between the nasoturbinal and the septum, is a narrow recess which will be referred to as the "dorsal recess". Extending laterally between the nasoturbinal and the first endoturbinal is a large "lateral recess" of the nasal cavity into which project three ectoturbinals (Figs. 3–8) which are here termed the upper, middle, and lower ectoturbinals. The upper and lower are large processes bearing an extensive area of olfactory epithelium. The middle ectoturbinal is a small process attached to the middle of the lateral wall of the lateral recess. Lateral to the third endoturbinal there may be an additional small ectoturbinal.

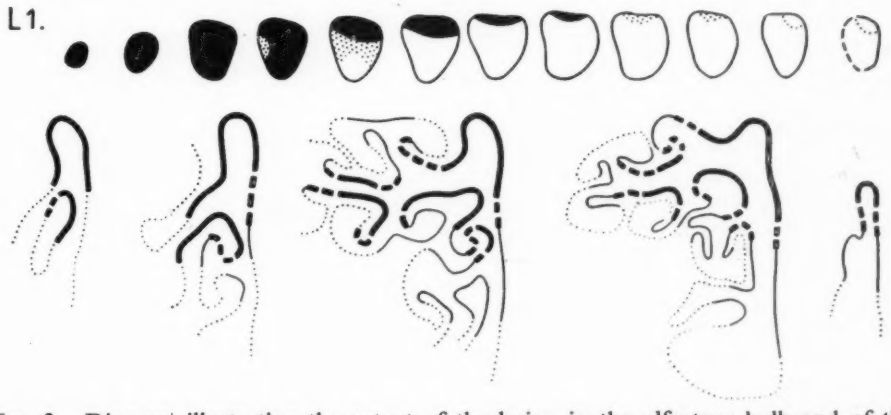

FIG. 3.—Diagram illustrating the extent of the lesion in the olfactory bulb and of the secondary degeneration of the olfactory epithelium in experiment L.1.

In Figs. 3–8 areas of severe degeneration of the olfactory epithelium are indicated by a continuous thick line, and of moderate degeneration by an interrupted thick line. Areas of apparently normal (or nearly normal) epithelium are indicated by a continuous thin line. Dotted lines represent the non-olfactory part of the nasal mucous membrane.

Twelve transverse sections of the olfactory bulb, taken at regular intervals, are represented above. The extent of total destruction is indicated in black and areas of partial involvement in stipple. In all cases the lateral aspect of the bulb is shown to the left. Below are shown, from left to right, outlines of transverse sections taken at regular antero-posterior intervals through the nasal cavity of the affected side, the septal epithelium in each case being shown to the right.

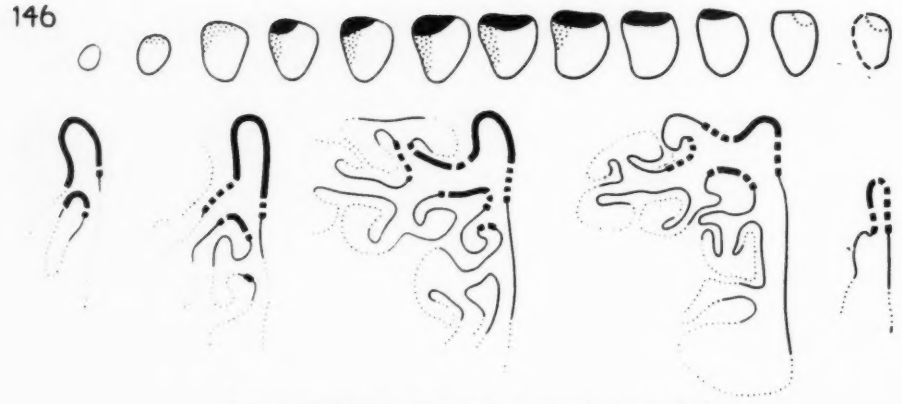

FIG. 4.—Diagram illustrating experiment R.146.

In Figs. 3–8 areas of severe degeneration of the olfactory epithelium are indicated by a continuous thick line, and of moderate degeneration by an interrupted thick line. Areas of apparently normal (or nearly normal) epithelium are indicated by a continuous thin line. Dotted lines represent the non-olfactory part of the nasal mucous membrane.

Twelve transverse sections of the olfactory bulb, taken at regular intervals, are represented above. The extent of total destruction is indicated in black and areas of partial involvement in stipple. In all cases the lateral aspect of the bulb is shown to the left. Below are shown, from left to right, outlines of transverse sections taken at regular antero-posterior intervals through the nasal cavity of the affected side, the septal epithelium in each case being shown to the right.

Results

Experiment L.1 (Fig. 3).—At operation, approximately the anterior third of one olfactory bulb was removed and the animal killed five weeks later. Serial sections show that the lesion is fairly well circumscribed but, presumably as the result of vascular interference, a narrow zone of necrosis extends back on the upper surface of the bulb as far as the junction of its middle and posterior thirds. Except in the neighbourhood of the main lesion, the glomerular formations of the remaining part of the bulb appear normal.

Serial sections through the nasal cavity show severe degeneration of the olfactory epithelium extending through the whole extent of its dorsal part. It affects the lining of the dorsal recess, approximately the dorsal half of the septum, the greater part of the nasoturbinal, the dorsal and medial aspects of the first and second endoturbinals, and the opposed surfaces of the upper and lower ectoturbinals. These areas are bordered by fairly wide zones of moderate degeneration. The olfactory epithelium appears to be normal over the lower half of the posterior part of the septum, the greater part of the third endoturbinal, the whole of the fourth endoturbinal, and the middle ectoturbinal. Fig. 3 shows some correspondence between the position of the bulbar lesion and the area of secondary degeneration of the olfactory epithelium, but the correspondence is no more than approximate. The relative extent of this area appears greater in the more anterior sections, but it reaches back to the most posterior part of the nasal cavity. The septal epithelium is affected in part throughout its antero-posterior extent even though the medially situated glomeruli in the posterior half of the bulb are apparently normal. On the other hand, the absence of definite degeneration over the lower half of the posterior part of the septum, and the fourth and most of the third endoturbinals, is presumably related to the fact that, in general, they project on to the lower and caudal parts of the bulb. The unaffected parts of the ectoturbinal epithelium evidently have a similar projection.

Experiment R.146 (Fig. 4).—The intention in this experiment was to place a lesion limited to the lateral half of one olfactory bulb. Serial sections of the bulb show that it was mainly confined to the dorsal surface over the greater extent of the bulb, but there is a considerable cellular infiltration in the lateral surface of the anterior half of the bulb and the glomeruli in this region are grossly shrunken (though only the most dorsally situated are completely destroyed). On the other hand, the medially situated glomeruli appear normal. The olfactory ventricle is greatly distended.

The serial sections of the nasal cavity show severe degeneration of the epithelium lining the dorsal recess, and of that covering the upper part of the septum, the whole length of the nasoturbinal, and the upper surface of the first endoturbinal. A moderate degree of epithelial degeneration is present over the medial part of the upper ectoturbinal and a narrow zone on the upper surface of the second endoturbinal, as well as alongside the margins of the severely degenerated areas. There is a broad relationship between the dorsally situated lesion of the bulb and the limitation of the epithelial degeneration mainly to the upper part of the nasal cavity. On the other hand, the involvement of the laterally situated glomeruli is not reflected in much degeneration of the lateral areas of olfactory epithelium. Compared with the previous experiment, L.1, the epithelial degeneration is not so extensive or severe over the anterior extremities of the first endoturbinal, the nasoturbinal, or the upper ectoturbinal. This is evidently related to the fact that the anterior quarter of the olfactory bulb was left almost intact. In some areas, particularly over the first endoturbinal (Fig. 9), the junction between severely degenerated and apparently normal epithelium is quite abrupt, suggesting that here the regional projection on to the bulb may be rather precise.

Experiment R.634.—A small lesion was made in the frontal half of the dorsal surface of one olfactory bulb, and the animal killed two weeks later. Serial sections show that the lesion is very limited, involving a narrow strip of the dorsal aspect of the bulb and extending back almost to the level of the accessory bulb. It corresponds closely to that of the previous experiment (R.146) but without the involvement of the laterally situated glomeruli.

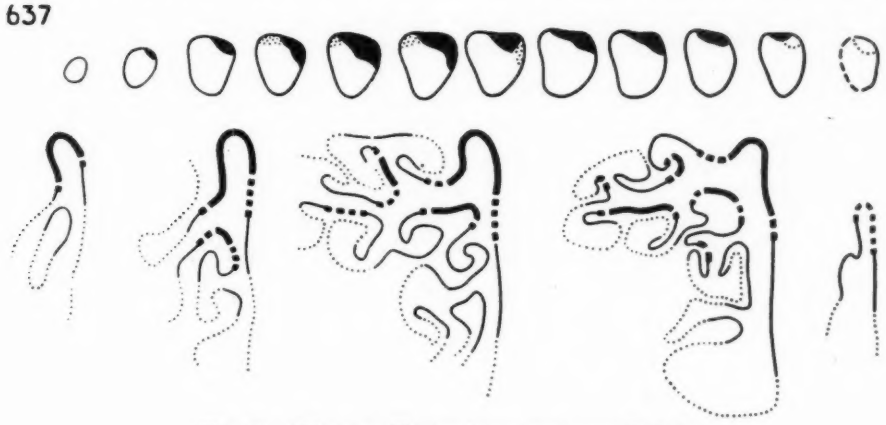

FIG. 5.—Diagram illustrating experiment R.637.

The serial sections of the olfactory cavity are somewhat imperfect, but they permit a satisfactory delineation of the areas of epithelial degeneration. The distribution of the degeneration conforms closely to that of experiment R.146, except that it extends further down on the septum (particularly anteriorly), is less marked on the upper aspect of the first endoturbinal, and does not appear to involve the second endoturbinal at all. At the most posterior extremity of the nasal cavity there is little evidence of degeneration except for a moderate degree near the upper margin of the septum and the lateral wall of the dorsal recess.

Experiment R.637 (Fig. 5).—A lesion was made on the medial aspect of the anterior half of one bulb. The animal was killed two weeks later. Serial sections show that, probably as the result of vascular damage, a zone of necrosis extends back from the site of the operative lesion on the dorsal aspect of the bulb. They also make it apparent that the lesion had not involved as much of the medial aspect of the glomerular system as had been intended.

Sections of the nasal cavity show that the distribution of the epithelial degeneration is somewhat similar to that of the previous experiments, but rather more extensive. For example, it involves more of the ectoturbinal epithelium even though the laterally situated glomeruli were less affected by the lesion than in experiment R.146. The degeneration of the septal epithelium also extends further down over the more posterior part of the septum. The epithelium covering the second, third, and fourth endoturbinals shows no gross evidence of degenerative change. This, together with the absence of evident degeneration over the whole extent of the lower half of the septum, makes it clear that there is some degree of dorsi-ventral projection from the olfactory epithelium to the olfactory bulb.

Experiment R.638 (Fig. 6).—In this case the lesion was mainly limited to the anterior third of one bulb. The animal was killed two weeks after the operation. The posterior extension of the lesion was found to be considerably less than in any of the four previous experiments. In conformity with this, the retrograde degeneration of the olfactory epithelium is also less extensive, and in the most posterior sections it shows no gross change. Nevertheless, the distribution of the degeneration is considerably wider than would be expected on the basis of a sharply localized topical projection on to the bulb. Over the upper part of the septum in its anterior two-thirds, a corresponding extent of the nasoturbinal, the convexity of the upper ectoturbinal, and the upper surface of the whole length of the first endoturbinal, the olfactory epithelium shows severe degeneration. A moderate degree of degeneration is also present over the upper surface of the lower ectoturbinal and in marginal zones bounding the strips of severe degeneration. It will be noted (Fig. 6) that the epithelium at the summit of the dorsal recess is represented as being not obviously degenerated. However, it is not possible to make any definite statement about this region, because the corresponding olfactory epithelium of the opposite side shows some shrinkage (? of rhinitic origin), which thus precludes a comparison with the operated side. Compared with experiment R.637 the epithelial degeneration extends further forward

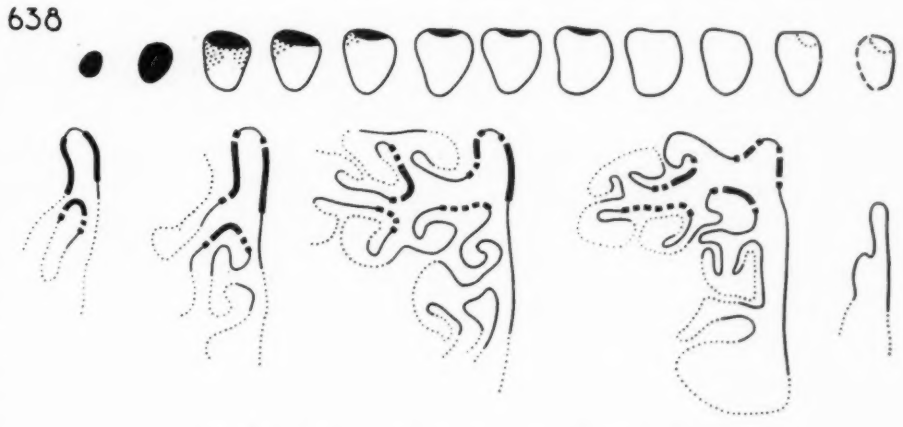

FIG. 6.—Diagram illustrating experiment R.638.

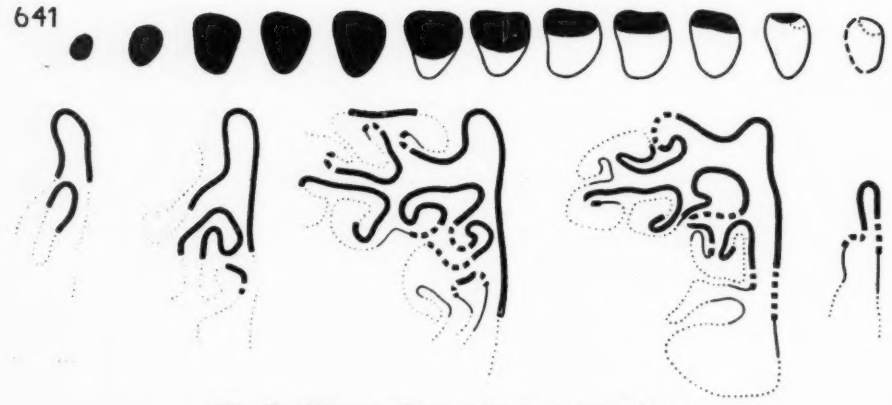

FIG. 7.—Diagram illustrating experiment R.641.

In Figs. 3–8 areas of severe degeneration of the olfactory epithelium are indicated by a continuous thick line, and of moderate degeneration by an interrupted thick line. Areas of apparently normal (or nearly normal) epithelium are indicated by a continuous thin line. Dotted lines represent the non-olfactory part of the nasal mucous membrane.

Twelve transverse sections of the olfactory bulb, taken at regular intervals, are represented above. The extent of total destruction is indicated in black and areas of partial involvement in stipple. In all cases the lateral aspect of the bulb is shown to the left. Below are shown, from left to right, outlines of transverse sections taken at regular antero-posterior intervals through the nasal cavity of the affected side, the septal epithelium in each case being shown to the right.

on the first endoturbinal, presumably in relation to the fact that the anterior extremity of the olfactory bulb had been completely destroyed.

Experiment R.641 (Fig. 7).—At the operation a lesion was made involving the anterior two-thirds of one olfactory bulb, and the animal was killed six weeks later. Serial sections show that approximately the anterior half of the bulb had been completely removed, while in the posterior half a considerable proportion of the dorsal glomeruli had been destroyed.

The olfactory epithelium shows an extensive distribution of severe degeneration. This involves the whole of the septal epithelium (with the exception of the most ventral portion posteriorly), practically the whole length of the first and second endoturbinals (except along their attached margins where the degeneration is moderate), the roof of the lateral nasal recess, the upper and lower ectoturbinals, and almost the entire surface of the nasoturbinal. The epithelium of the third endoturbinal shows degeneration over its upper surface. That covering the fourth endoturbinal and the small middle ectoturbinal appears to be intact.

A careful study of the olfactory epithelium where it appears unaffected, for example, at the lower margin of the posterior end of the septal area, and over the fourth endoturbinal, with special reference to its relative depth, its cell density, and histological traces of cytolysis, fails to show evidence of even a partial degeneration. It seems probable, therefore, that these areas project entirely, or almost entirely, on to the ventral part of the posterior half of the bulb. This evidence for a form of localized projection, based on the connexions of a relatively small region of the bulb left intact after destruction of the greater part, is perhaps more convincing than in those experiments in which the bulbar lesion has been of very limited extent. For in the latter experiments it is not easy to assess the amount of indirect involvement of glomerular connexions beyond the immediate boundary of the primary lesion.

Experiment R.642 (Fig. 8).—In this experiment one bulb was almost completely destroyed except for the medio-ventral part of its posterior third. The animal was killed six weeks after the operation. Serial sections show that even those glomeruli spared by the main lesion are not all intact, for in the neighbourhood of the lesion many are grossly shrunken, presumably as the result of a partial or complete interruption of their olfactory fibre connexions.

Almost the whole extent of the olfactory epithelium shows severe degeneration. The only region which shows no evidence of degenerative changes is the lower margin of the septal area and the lateral wall of the nasal cavity at the extreme posterior end of the latter, and a small strip on the under surface of the third endoturbinal. A moderate degree of degeneration affects the lower margin of the septal area in the posterior

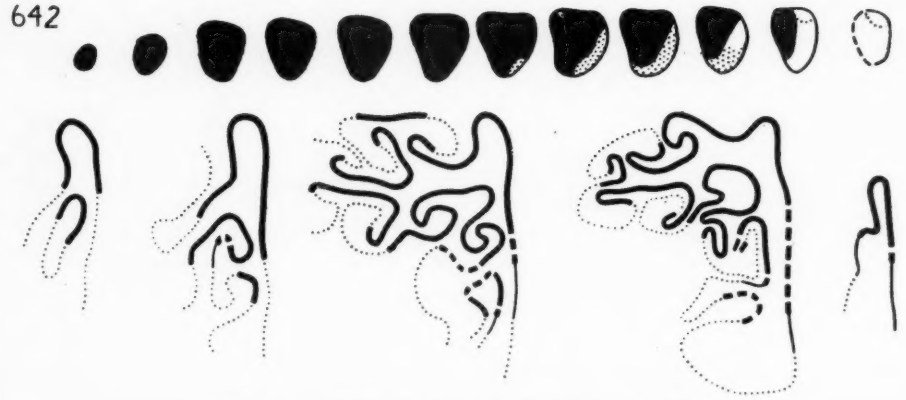

FIG. 8.—Diagram illustrating experiment R.642.

half of its extent, the lower surface of the second endoturbinal, the upper lip of the third endoturbinal, and the epithelium covering the fourth endoturbinal. The distribution of the epithelial degeneration is thus similar to that of the previous experiment (R.641) but rather more extensive.

Experiment R.644.—The lesion in this case was similar to that of the previous experiment (R.642). The animal was killed six weeks after the operation, and serial sections of the bulb show complete destruction except for the medially situated glomeruli in the posterior third of the bulb.

The serial sections through the nasal cavity are not entirely satisfactory, for the mucous membrane is affected by scattered patches of atrophic rhinitis. However, where the epithelium appears normal in structure it provides some reliable information regarding the distribution of secondary degeneration following the bulbar lesion. The extent of this degeneration corresponds closely with that in experiment R.642. It involves the whole of the septal epithelium, except the ventral part of its most posterior portion. The epithelium covering the medial aspect of the third and fourth endoturbinals also appears to be intact. On the other hand, the epithelium of the lateral wall of the nasal cavity has undergone severe degeneration throughout its whole antero-posterior extent.

Discussion

It is quite evident, from the results of the experiments recorded above, that there is some degree of spatial localization in the olfactory bulb in the sense that the upper areas of the olfactory epithelium project mainly on to the upper part of the bulb, and vice versa. The experiments also provide some evidence that the more anterior and posterior areas tend to project on to the more anterior and posterior regions of the bulb respectively, but here the relationship appears to be more diffuse. In experiment L.1, for example, where the posterior part of the bulb had been left intact, severe degeneration of the epithelium was found to extend back to the posterior extremity of the dorsal recess, while in experiments R.146 and R.637, where the anterior part of the bulb had escaped the lesion, severe degeneration extended to the anterior extremity of the dorsal recess and the nasoturbinal. In a mediolateral direction also, the topographical projection of the olfactory epithelium on to the bulb seems to be not very sharply defined, though the experiments again provide evidence for a regional projection of some degree in this direction.

If the projection of different areas of the olfactory epithelium is considered separately, the following general statements appear to be justified by the experiments. The dorsal part of the septal epithelium projects mainly on to the dorsally situated glomeruli, and the more ventral part to those situated medially and ventrally. The epithelium covering the nasoturbinal likewise projects largely on to the dorsal glomeruli, though there is some evidence that the more lateral region of this epithelium is predominantly related to the glomeruli on the lateral surface of the bulb near its upper margin. The epithelium covering the dorsal surfaces of the first and second endoturbinals (particularly the former) appears to be most directly related to the front and upper parts of the bulb, while that covering the less exposed areas of these processes only undergoes degeneration

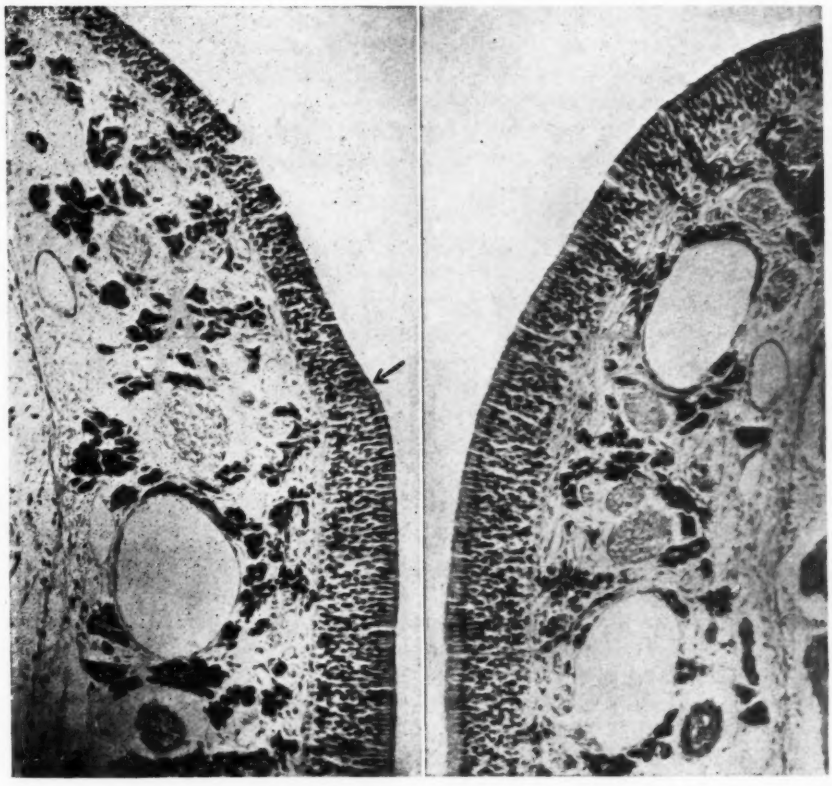

FIG. 9.—Sections of the olfactory epithelium covering the first endoturbinal in experiment R.146 on the operated side (*a*) and the normal side (*b*). (× 120.) On the operated side the arrow marks the abrupt transition between apparently normal epithelium and severely degenerated epithelium.

as the result of extensive lesions involving the more ventral and posterior regions of the bulb. The epithelium of the third and fourth endoturbinals is evidently related predominantly to the glomeruli in the most postero-ventral part of the bulb. As regards the epithelium covering the ectoturbinals in the lateral recess of the nasal cavity, the experiments suggest that the more exposed parts tend to project on to the more dorsal glomeruli, and the less exposed parts on to ventral and lateral glomeruli.

It is not possible to draw more precise conclusions on the topographical localization in the olfactory bulb from these experiments, because the material only permits an approximate delineation of the extent of the lesion, complete or partial, affecting different glomeruli; nor does it afford a very exact quantitative evaluation of the degree of secondary degeneration affecting the receptors in different parts of the olfactory epithelium. In general, however, the type of localization which has been demonstrated accords reasonably well with that which has been reported by Adrian on the basis of electro-physiological studies. That the projection, in relation to at least some areas of epithelium, may perhaps be more precise than the present series of experiments indicates, is suggested by the observation that in certain cases of partial lesions of the bulb the transition between apparently normal and severely degenerated areas of epithelium is rather abrupt. This appearance is shown in Fig. 9, in which the olfactory epithelium covering the first endoturbinal in experiment R.146 is seen on the operated and normal sides. In this particular case it is difficult to explain the abruptness of the transition between the two epithelial areas except on the assumption that the junctional margin of the corresponding projection areas in the olfactory bulb is equally well defined.

That there is no regular point-to-point projection of the olfactory epithelium on to the bulb, in the sense that, as with the projection of the retina on to the lateral geniculate nucleus, each local area of the sensory epithelium is represented centrally in an orderly sequence of equivalent areas having the same spatial relationship, seems assured by a histological study of normal material. It is now established that the olfactory fibres derived from the receptors in the olfactory epithelium pass directly up to the cribriform plate in parallel fasciculi, and without any significant rearrangement while they are in the nasal cavity. But as soon as they penetrate the cribriform plate to enter the cranial cavity, the individual fasciculi split up into smaller components and the latter become involved in a most complicated plexus of interweaving fibres on the surface of the olfactory bulb before they enter the latter. It appears certain, therefore, that the spatial relationship of the nerve fibres within the nasal cavity is by no means preserved up to the actual site of their entrance into the bulb. For example, in protargol-treated sections, some fibres approaching the anterior tip of the bulb from a more ventral direction in the nasal cavity may be seen crossing those coming from a more dorsal direction so as to reach the dorsal aspect of the bulb, and vice versa. An examination of individual glomeruli, also, shows olfactory fibres approaching and entering them

FIG. 10.—Section of a normal olfactory bulb of a rabbit stained with protargol, showing adjacent glomeruli receiving bundles of olfactory fibres entering from different directions. Above the glomeruli is seen the outer molecular layer of the bulb, traversed by the dendrites of mitral cells. (× 210.)

from many different directions. Two such examples are shown in Figs. 10 and 11, and in the latter the intricacy of the plexus of olfactory fibres on the surface of the bulb is made very apparent. Clearly, this plexiform arrangement is the occasion for a resorting of olfactory fibres which makes it possible for some or all the glomeruli to receive impulses from different areas of the olfactory epithelium not necessarily in direct topographical relationship to each other, and it may be surmised that this is in some way associated with functions of olfactory discrimination. One possibility is that there are different types of olfactory receptor which are differentially susceptible to various forms of olfactory stimulus, and that impulses from the several categories of receptor become segregated and conveyed to different glomeruli of corresponding categories. On the other hand, as Adrian has pointed out, there is no evidence as yet that the olfactory epithelium is composed of anything like a uniform mosaic of different kinds of receptor each with specific affinities for certain kinds of odoriferous substances, though the possibility of some such organization is not necessarily precluded by the methods at present available for the analysis of olfactory impulses reaching the bulb. Another possible interpretation of the resorting of olfactory nerve fibres is that those derived from equivalent regions of the complicated turbinal system (for example, from the more exposed surfaces or from the deeper and less immediately accessible recesses) are regrouped so as to be led to different sets of glomeruli. Such an arrangement would be consistent with Adrian's suggestion that olfactory discrimination may depend, at least in part, on a regional excitation of the olfactory epithelium by the differential diffusion of odoriferous substances of varied molecular size. This suggestion involves the consideration that the complicated system of turbinate processes in animals such as the rabbit is not simply a device for increasing the surface extent of the olfactory epithelium, but may be an important factor in determining the direction followed by odoriferous particles having differential rates of diffusion, so as to lead to specific spatial patterns of stimulation of the epithelium. This hypothesis is particularly attractive since it eliminates the need for postulating the existence of olfactory receptors of many different types. However, one theoretical difficulty which presents itself is that an intricate folding of the olfactory epithelium itself is evidently not an essential prerequisite for olfactory discrimination. In man, for example, the olfactory epithelium is not involved in the labyrinthine convolutions found in most lower mammals, for it is here represented by two approximately flat sheets covering the upper third of the septum and the medial surface of the superior concha. Yet man is capable of an astonishingly high degree of olfactory discrimination, even though his olfactory sensitivity may be considerably less than that of lower mammals. It is possible that olfactory discrimination depends on several different factors, of which a spatial pattern of stimulation of the olfactory epithelium is but one. In any case, whatever the peripheral analytical mechanism for olfactory discrimination may be, on anatomical grounds the glomeruli of the olfactory bulb appear to provide a suitable basis as a series of central analysers, for, apart from the fact that some of the small periglomerular cells may permit a certain degree of functional interaction between immediately adjacent glomeruli, each glomerulus with its connecting mitral cells forms virtually a closed system.

FIG. 11.—Section of a normal olfactory bulb of a rabbit stained with protargol showing a glomerulus receiving olfactory fibres which enter it from opposite directions. Below the glomerular layer is seen part of the complicated plexus of olfactory fibres on the surface of the bulb. Entering the large glomerulus from above are seen numerous dendrites of mitral cells. (× 210.)

Thus, through the individual glomeruli separate groups of impulses from the olfactory epithelium may be segregated as far as their termination in the prepiriform cortex and adjacent regions of the cerebral hemisphere.

It would clearly be desirable, in connexion with the problem of olfactory discrimination, to obtain much more precise information regarding spatial localization in the olfactory bulb than has been possible with the methods used in the experiments recorded here. This could no doubt be done by effecting more sharply circumscribed lesions limited to localized groups of glomeruli (using such methods as thermocoagulation), and defining more precisely the degree and extent of the ensuing degeneration in the olfactory epithelium by making accurate counts of individual receptors in silver-impregnated preparations. Technically this presents a somewhat formidable task, but it should make it possible to determine just how far the localized projection of different areas of the olfactory epithelium on to the olfactory bulb is theoretically capable of providing a basis for olfactory discrimination.

Summary

The distribution of secondary degeneration in the olfactory epithelium following lesions of the olfactory bulb has been studied in a number of rabbits.

The experiments show that there is some degree of spatial localization in the projection of different areas of the olfactory epithelium on to different regions of the bulb.

The evidence suggests that, although the projection as a whole is of a somewhat diffuse type, in regard to some areas of the olfactory epithelium it may be rather precise.

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OBSERVATIONS ON THE PASSAGE OF WEED'S PRUSSIAN BLUE MIXTURE ALONG THE AXIS CYLINDERS AND INTER-FIBRE FLUID OF NERVES

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The idea that the axis cylinder is the path by which the causal agent of rabies reaches the central nervous system after peripheral inoculation is of considerable antiquity. Duboué (1879) is stated by Gamaleia (1887) to have urged axonal transmission to the complete exclusion of other pathways. In more recent times experimental support for this pathway has been forthcoming from Goodpasture and Teague (1923) working with herpes, Goodpasture (1925) working with rabies, and Fairbrother and Hurst (1930) working with poliomyelitis. More direct visual evidence was adduced by Perdrau (1937) who studied the passage of a number of "dyes" especially Weed's solution (a mixture of potassium ferrocyanide and iron ammonium citrate) along nerves both *in situ* and when excised. Using a weak cataphoresis current Perdrau found that this mixture could pass some 4 to 5 cm. along the sciatic nerve in four hours. He also demonstrated the passage of the solution into the spinal cord where a selective staining of some anterior horn nuclei took place. Moreover he claimed that the dye permeated axis cylinders selectively, though staining of the connective tissue sheaths of the nerve also took place. With colloidal solutions, for example, Victoria blue, no trace of impregnation of axis cylinders was obtained. In a critical review of axonal transmission Doerr (1939) emphasizes this failure to impregnate the axis cylinder by colloidal solutions (more nearly related to virus particles than are true solutions) and also the staining of the connective tissue sheaths. Since Perdrau did not consider passage by diffusion in the interfibre fluid, though some of his findings would seem to be most readily explicable on this basis, the present work, largely a repetition of his, was undertaken.

Material and Methods

Four experiments were carried out on the sciatic nerve *in situ* in the rabbit anaesthetised with nembutal, and 11 further experiments on lengths of sciatic nerve excised in continuity with the lumbar cord. In three additional experiments rat sciatic nerve was used. In the first group the sciatic nerve was exposed at mid-thigh level, freed for about one centimetre, divided with a sharp razor blade, and the epineurium picked up with a fine oiled black silk suture on an eyeless needle. By this means the proximal end of the nerve was threaded for about 5 mm. into a capillary glass tube suitably bent so that it could be readily fixed *in situ* when the posterior thigh muscles were brought together. Perdrau's injunction to obviate all kinking or compression of the nerve was found to be most important. A 10% mixture of sodium ferrocyanide and iron ammonium citrate made up in Ringer's solution was introduced by a needle into the open end of the glass tube so that the 5 mm. of nerve within was bathed in the mixture. Considerable difficulty was experienced in preventing a "creep" of fluid between the nerve and the capillary tube. After some trials the tube was filled with fine sawdust kept saturated with the solution. The spinal cord was exposed through a small lumbar laminectomy, and a nonpolarisable (Ag–AgCl) electrode was placed in contact with its surface. Another was introduced into the open end of the capillary tube, this latter being connected up to the negative pole of a battery and the cord electrode to its positive pole. The voltage applied was adjusted so that a current of 0·3–0·5 milliamp flowed in the circuit. The cord contact was kept moist otherwise this current fell markedly. Experiments were continued for six to eight hours, more anaesthetic being given as required. At the end of that time the nerve was dissected out in continuity with the cord and fixed in 1% HCl in 10% formol for 24 hours. In the series of experiments carried out on the excised nerve cataphoresis was employed in seven cases. In four of these the length of nerve attached to the cord was short—about 1·5 cm.

Several further experiments were made to determine the permeability of the intact and damaged epineurium to prussian blue mixture. Lengths of nerve were excised between fine ligatures and in some cases a deliberate trauma was inflicted to breach epineurial continuity about the middle of the nerve segment. In others a short segment was cleaned of epineurium as far as possible under the microscope so that only a minimal

connective tissue investment remained in this region. The pieces were immersed in the dye mixture for periods of four to six hours.

All specimens after fixation were embedded in paraffin, sectioned at 7–10μ, and stained with carmalum.

Observations

Impregnation of axis cylinders was never so extensive as that observed by Perdrau (1937). Thus after six hours' cataphoresis there was staining of connective tissue sheaths for some 4 cm. above the point of immersion of the nerve and coloration was not visible under the microscope above the level at which definite naked eye coloration ceased. Immediately above the immersed nerve segment there was diffuse staining of all the elements of the nerve. In the thin microscopic section the blue coloration of the epineurium, so readily visible to the naked eye in the gross specimen, was quickly lost. The diffuse blueness of the nerve fibres also faded quickly as one passed up the nerve and short sections of intensely stained nerve centred on the nodes of Ranvier stood out (Fig. 1a), the internodes becoming at first very faintly stained and then not noticeably coloured. Sometimes an annular effect was observed (Fig. 1b). In general, stained nodes were met with close up against the epineurium rather than in the depths of the nerve. The prussian blue seemed often to spread more readily in the circumferential part of the nerve (Fig. 2). Between the intensely staining nodes of Ranvier the axis cylinders remained apparently free from colour. From these appearances no unequivocal conclusions could be drawn about the selective passage of the prussian blue mixture up the axis cylinders from their severed ends. Indeed, the collar of dyestuff shown in Fig. 1b might equally be interpreted as resulting from the diffusion of prussian blue in the thin film of interfibre fluid with staining of axis cylinders at points where they are accessible to the fluid, i.e., the nodes of Ranvier. The fact that the nodes are stained higher up the nerve in its circumferential part supports this view, for the subepineurial space might be expected to allow more ready diffusion of dye (Brierley and Field, 1949, Fig. 6d). Perdrau (1937) remarked on the blue ring often to be seen at the nodes of Ranvier, and his description would seem to imply acceptance of the spread of the prussian blue other than along the axis cylinders, though he makes no mention of interfibre fluid. The system of capillary spaces within a nerve would seem to present the necessary conditions for the operation of powerful electrophysical forces which might result in surface streaming over nerve fibres. A phenomenon which offers certain points of analogy has been recorded by McFarlane (1940) who found that when a buffered suspension of vaccinia virus was placed in a Tiselius U-tube, the virus particles showed a streaming along the centre of the tube whilst the buffer moved in the opposite direction. In some parts of the present material appearances suggestive of diffusion along the neurilemmal surface were encountered (Fig. 3). Here fibre surfaces are stained by prussian blue which outlines well the nodes of Ranvier while the axis cylinders are only feebly coloured. Why nodes should stain so intensely and almost selectively when the concentration of prussian blue is low is not known. It may be that the interval between myelin segments accommodates interfibre fluid from which the prussian blue is thrown down on acidification. However, the nodes of Ranvier are known to possess special electrical properties (Tasaki and Mizuguchi, 1948) and it is possible that a high ferrocyanide ion concentration is held in their vicinity.

Perdrau's finding that impregnation of a piece of lumbar cord through an attached nerve root may lead to a marked staining of certain nuclei of anterior horn cells is easily confirmed (Fig. 4), though this could not be achieved if the length of nerve attached to the cord exceeded 1·5 cm. On the other hand his finding that the nuclei of dorsal root ganglion cells do not take up the mixture is subject to qualification, for no difficulty was experienced in achieving such impregnation provided that a short nerve root was used (Fig. 5). Perdrau was able on rare occasions to trace a coloured axis cylinder from the surface of the cord up to the stained anterior horn cell. This has never been possible in the present material. Naturally the success of nuclear impregnation depends upon the concentration of prussian blue which reaches the neighbourhood of the nuclei. A low concentration may stain the nucleolus alone, but that a high concentration leads to the intense staining is shown in Fig. 4. It has been found that in an area containing several well stained anterior horn nuclei careful oil immersion examination reveals a sparse, fine, dust-like deposit of prussian blue, staining no element selectively. The appearances in the cord would appear to result therefore from the especial affinity of certain anterior horn nuclei and nucleoli for the prussian blue mixture which diffuses non-selectively throughout the cord substance.

Discussion

The main findings reported by Perdrau (1937) with regard to the passage of prussian blue mixture along nerves, especially when aided by cataphoresis, have been confirmed. While there can be no doubt that axis cylinders do take up the prussian blue

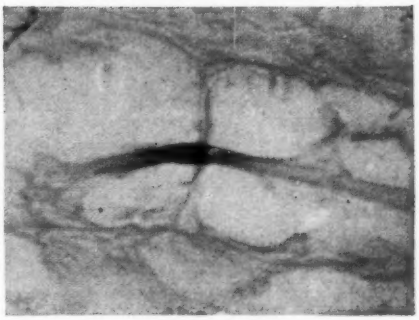

FIG. 1*a*

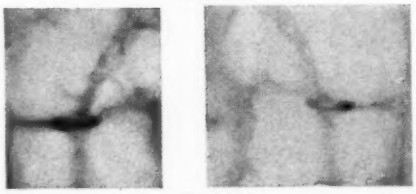

FIG. 1*b*

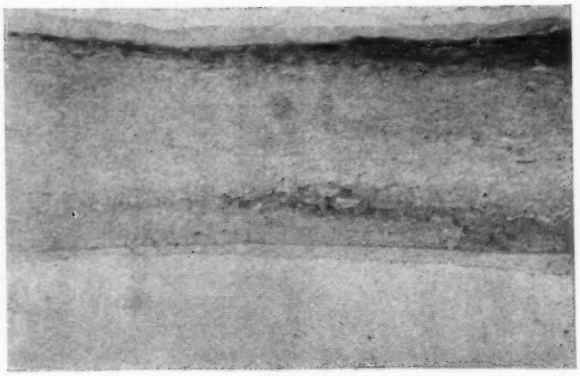

FIG. 2

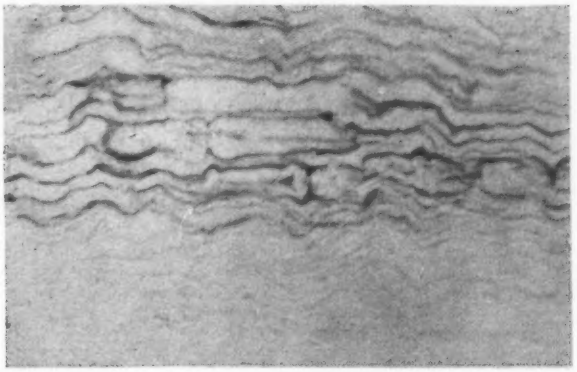

FIG. 3

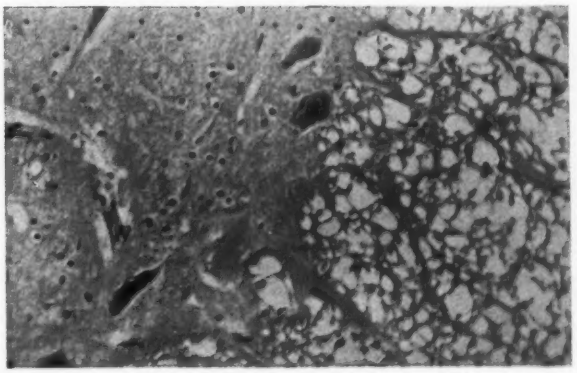

FIG. 4

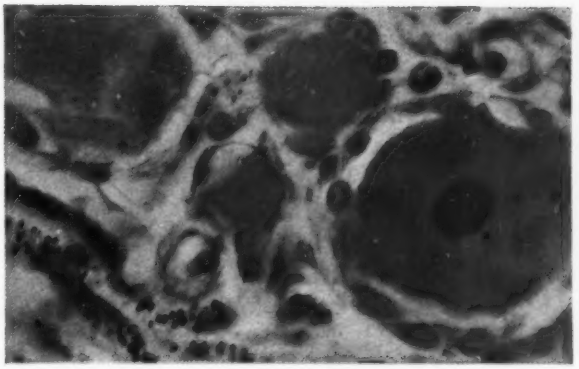

FIG. 5

FIG. 1 *a*.—Deeply stained node of Ranvier in rabbit sciatic nerve about 1·5 cm. above point of immersion in Weed's solution. × 1180.

FIG. 1 *b*.—"Collar" of prussian blue around axis cylinder at node of Ranvier. About 2 mm. above Fig. 1 *a*. × 1180.

FIG. 2.—Sciatic nerve of rabbit about 1·5 cm. above immersion level after six hours' cataphoresis. Note diffusion of the prussian blue in peripheral parts of the nerve. × 40.

FIG. 3.—Same section as Fig. 2. Note prussian blue outlining the nerve fibres and dipping in between myelin segments at nodes of Ranvier, and the faintly coloured axis cylinders. × 300.

FIG. 4.—Transverse section of lumbar cord impregnated through an attached sciatic nerve root (1·5 cm.) by cataphoresis. Several nuclei have taken up prussian blue whilst neighbouring ones are quite uncoloured. × 120.

FIG. 5.—Cell of lumbar dorsal root ganglion impregnated by cataphoresis. Note dense coloration of nucleus and particles of prussian blue on surface of nerve fibres in lower part of figure. × 650.

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mixture readily the appearances do not seem to afford conclusive evidence that permeation takes place exclusively through the axis cylinder for any length. There is evidence that diffusion processes are active in the interfibre capillary spaces and in the subepineural region. In addition there is a surface creep in the epi- and peri-neurium. The results of immersing isolated nerve segment into prussian blue mixture suggest that a thick, intact epineurium will prevent staining of subjacent nerve fibres. However, if a segment of nerve is well stripped at one spot so that only a thin, investing connective tissue sheath remains, permeation readily takes place locally and spreads up and down the nerve. The connective tissue sheath would seem, therefore, to exert normally a mechanical protective action adequate to prevent the observed results being due to inward diffusion of the prussian blue mixture.

It is interesting to recall that Römer (1913) in considering the spread of intracerebrally inoculated virus suggested that it might spread most easily along the " lymph channels accompanying the neurone ". From the context it is evident that the channels he had in mind are analogous to the interfibre capillary spaces along which prussian blue has been observed to spread in the present work. It is along these spaces too that Marinesco and Dragonesco (1923) suggest that the virus of herpes fibrilis may spread from the cornea to infect the brain. These spaces can be readily shown up by the intraneural injection of india ink (Brierley and Field, 1949) or herpes virus (Field, 1950). In this latter case columns of lymphocytes and cells showing nuclear fragmentation are to be found between individual nerve fibres. According to Weiss (1943) there is a definite centrifugal motion of the interfibre fluid which would make it a poor vehicle for centripetal transport of particulate matter in the nerve. This according to Weiss affords added, though indirect, support to the theory that such afferent transport, expecially of neurotropic viruses proceeds within rather than between nerve fibres. However, the existence of a centrifugal flow such as that envisaged by Weiss does not of necessity exclude centripetal diffusion of particulate matter (Field and Brierley, 1948). Moreover Young (1945) has brought forward evidence which suggests that under normal conditions there may be a slow centrifugal streaming of axoplasm, and this, together with the fact that de Renyi (1932) demonstrated the axis cylinder to be possessed of a jelly-like consistency, offers indirect evidence against the axis cylinder as an important conducting element for particulate matter. Indeed, Hurst (1936) has conceded that " the chief difficulty in the general acceptance of [axonal transmission] lies in the physical constitution of the nerve fibre ".

Teale and Embleton (1920), although they believed that some soluble substances might diffuse up axis cylinders, concluded that the neural lymphatics and lymphatic spaces play an important part in the process. Orr and Rows (1916) also emphasized the " lymph stream in nerves " and their connective tissue coverings as important in the transport of toxins and bacteria to the central nervous system, and Ponomarew (1928) and Uljanow (1929) brought forward evidence of the centripetal passage of toxins and other soluble substances in the connective tissue spaces of nerves.

This brief and by no means exhaustive review is sufficient to show that the axis cylinder, the endoneurial fluid (contained in the interfibre or " lymph spaces " of the nerve), and the nerve sheaths have all been held either singly or in combination to be the essential avenue of invasion of the central nervous system through a peripheral nerve. The results described in the present work do no more than indicate that all three are possible in some measure under the given experimental conditions. Doerr's caution (1939) in translating such results to the problem of the neural transmission of viruses is well founded.

The nuclear impregnation in the spinal cord and dorsal root ganglia picking out certain cells to the exclusion of others nearby deserves further consideration. It is possible that affinity for prussian blue is dependent upon an electrical surface charge of the nucleus and the fact that this itself varies with different functional states of the nerve cell. It is an interesting speculation that the negative charge on the poliomyelitis virus particle may be the means whereby it is anchored in the first place to the anterior horn cell nucleus. If any valid analogy may be drawn from the findings with the negatively charged ferrocyanide ion complex, such a " fastening on " would be very patchy ; this is precisely what is found in the anterior horn cell degeneration of poliomyelitis. Moreover, Russell (1947) has established the influence of exercise on the localization and severity of paralytic poliomyelitis ; that is, the influence of the physiological state of the nerve cell on its liability to attack by the virus. It would seem to be a reasonable speculation that exercise may be a factor affecting electrical charge on the anterior horn nucleus.

Summary

Diffusion of a prussian blue mixture may take place in the axis cylinder, interfibre spaces, and connective tissue sheaths of a nerve.

No special conducting power of the axis cylinder was noted.

The nodes of Ranvier take up prussian blue and become intensely stained even when the concentration in the environment is below the threshold of visibility.

Certain nuclei of the anterior horn cells also have a high affinity for prussian blue, and the same has been found to be true of dorsal root ganglion cells.

The main views on neural transmission of crystalloids and viruses are indicated, and some speculations made on the significance of nuclear staining of the anterior horn cells.

I should like to express my gratitude to Professor J. M. Yoffey for his interest and encouragement in this work, and to Mr. K. Hunt and Miss M. Le Bechec for some of the histological preparations. For the colour photography I am indebted to Mr. J. E. Hancock and Mr. L. G. Cooper.

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A METHOD OF MEASURING REFLEX TIMES APPLIED IN SCIATICA AND OTHER CONDITIONS DUE TO NERVE-ROOT COMPRESSION

BY

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It is well known that in sciatica and other clinical conditions resulting from compression of a nerve root by a prolapsed intervertebral disc, disturbances of the tendon reflexes may occur. In sciatica, for instance, diminution or even absence of the ankle jerk is a common finding (Falconer, McGeorge, and Begg, 1948). Sometimes, however, this disturbance is slight and cannot readily be shown by the ordinary clinical tests. This investigation was therefore undertaken to assess the slighter degrees of impairment, and to elucidate its mechanism.

The knee jerk and the ankle jerk are each a true reflex involving only a monosynaptic pathway (Lloyd, 1943). The functional unit of reflex activity in skeletal muscle is, of course, the motor unit (Denny-Brown, 1929). It consists of a group of 100 or more contiguous muscle fibres innervated by a single motor neurone, which by its terminal branches, sends a nerve filament to the end-plate region of each of these muscle fibres (Clark, 1931 ; Weddell, Feinstein, and Pattle, 1944). When a whole muscle is stimulated reflexly, as when its tendon is stretched, its response is usually a submaximal motor twitch, for only some of the motor units respond, although they do so synchronously and once only. A brisk reflex response represents more motor units contracting than in the diminished reflex response. Since the motor units contract synchronously, and each in contracting contributes a small action potential, the sum of these action potentials is an index of the number of motor units involved in the reflex response. Thus the deflection recorded on the oscillograph gives a relative measure of the voltage, and can be used to compare one tendon reflex with the corresponding reflex of the opposite limb. In the present investigation, therefore, the oscillograph was used (*a*) to obtain the conduction time of tendon reflexes, (*b*) the conduction time past the compressed segment of a nerve root, and (*c*), within these limitations, a quantitative measure of the responses.

Methods of Investigation

Timing of Tendon Reflexes.—The reflex time was measured by an apparatus employing a specially-constructed percussion-hammer, surface electrodes placed over the muscle, and a double-beam oscillograph with a suitable amplifier to record the muscle response and also the time interval elapsing after the blow. All recordings were made in a shielded room. Button electrodes were chosen in preference to concentric needle electrodes, as they allow numerous points on the muscle to be examined without such discomfort as is caused by the intramuscular insertion of a needle electrode (Adrian and Bronk, 1929). In order to lower the electrical resistance of the skin, the surface electrodes with the concavity of each filled with electrode jelly were sealed over a small scratch (Richter, 1926). In this way an electrical resistance of less than 1,500 ohms was always obtained between any two electrodes. One electrode was placed over the appropriate muscle. The other was sealed to an inactive zone, for example, the tendon, or, what was found to be even more satisfactory, a bony point on the opposite limb. The electrical resistance of this arrangement was found to be less than that of a saline pad used as the indifferent electrode.

The percussion hammer was constructed of half-inch brass tubing in the form of a " T " piece (Fig. 1). The tubing acted as an electrical shield to the contact points situated within the head of the hammer, and all the necessary wiring was led from these contact points to the apparatus by means of shielded flex. A wooden piston, fitting loosely in one end of the head, was shaped to act as the striking edge of the hammer. The other end of this wooden piston rested against the metal contact

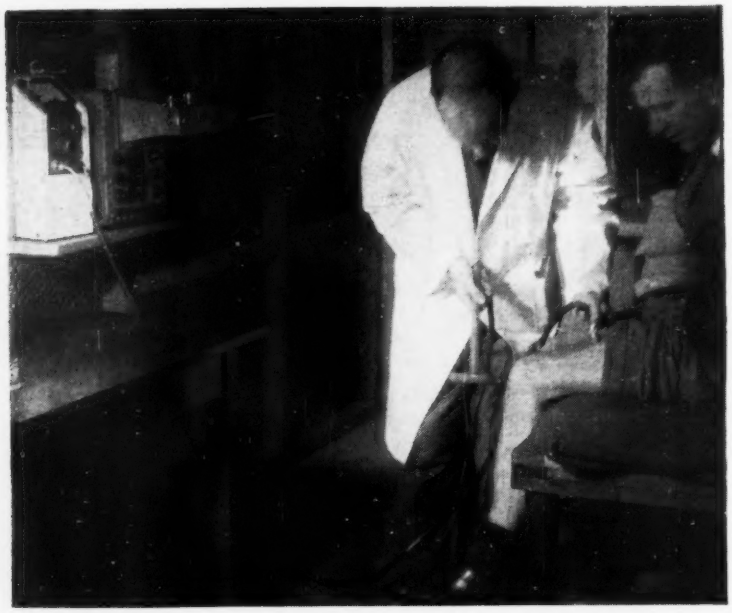

FIG. 1.—The interior of the screened room. The oscilloscope and amplifiers are on the left.

maker, and was adjusted so that any weight on the striking edge made an electrical contact, which triggered the sweep of the oscillograph.

One beam of the oscillograph was used for recording the muscle response, the other as a time marker recording 2 millisecond intervals. In order that the resting fluorescence of the oscillograph should not blur the photographic film, the resting position of the spots was placed on the extreme right, well off the fluorescent screen. The contacts in the head of the percussion hammer, when closed, caused the spot to fly across in 0·1 msec. to a position at the left of the screen. The spot then immediately returned to the right side at a slower and uniform speed, taking 50 msec. to complete the traverse. The fly-across was so fast that it left no trace on the photographs. The first evidence of the spot photographically and visually was obtained as it turned about on its slower return, and the records were all read from this point. The delay of 0·1 msec. in the beginning of the traverse was thus insignificant.

In interpreting the results, the muscle action potential was taken as indicating the arrival of the volley of nerve impulses at the muscle end-plates. Eccles and O'Connor (1939) have shown that after the arrival of the nerve impulse at the end-plates the muscle impulse is propagated down the muscle fibre at a speed of only 3 to 5 metres per second, and it precedes the contraction wave by about 1 msec. (Snyder, 1936). Thus a serious error would arise in the timing of the reflex if the muscle action potential were picked up anywhere other than at the end-plate. This delay in conduction within a muscle is partly compensated by the branching of the nerve and the dispersal of its axons within the muscle, and optimum results can usually be obtained if the electrode is placed over the belly of the muscle close to the point of nerve entry.

Where actual reflex times are stated in this paper they represent the average of at least six readings from one point on a muscle: the experimental error of the method was not greater than $\pm 0{\cdot}5$ msec.

Timing of Nerve Conduction Rates at Operation.—In some patients with nerve-root compression, whose tendon jerks had been timed pre-operatively, the conduction time in the affected nerve-root from the cauda equina to the muscle was measured at the operation undertaken for removal of the compressing lesion, and contrasted with the conduction time of the same nerve-root on the opposite side. Each patient was an example of compression of both ventral and dorsal nerves at a point immediately lateral to the theca by a prolapsed intervertebral disc. In each a laminectomy of one or two vertebrae was performed, but before the site of compression was disturbed the theca was opened. One or two nerve-roots on each side within the theca, including of course the root proximal to the site of compression, as well as its fellow of the opposite side as a control, were then isolated proximal to the lesion. Each nerve-root in turn was then stimulated submaximally with a single shock. For this purpose a sterilized triple-hook electrode was employed, the central electrode being the cathode, the outer two being anodes. The resulting response in the muscle was again recorded by surface electrodes, applied as described earlier. The whole apparatus was so arranged that a single stimulus could be given to the nerve root by a thyratron valve, and this stimulus also triggered the sweep of the recording oscillograph. For this part of the work the sweep speed of the beam was increased approximately two and a half times and thus the accuracy of the recordings was enhanced. This was made possible by the fact that the actual time interval to be measured was less than half that required for the reflex times: the longest reflex time recorded was 44 msec. compared with a maximum of 19·1 msec. in the direct stimulation experiments. The experimental error in this second

portion of the work was not greater than ±0·25 msec. In Table VI, which gives the actual times recorded, the results are stated as an average of at least six recordings made from each point on the muscle concerned. For the fourth lumbar root (L.4) the record was best obtained from the rectus femoris muscle, for the L.5 root from the tibialis anticus muscle or the extensor brevis digitorum muscle, and for the S.1 root, the gluteus maximus muscle, the soleus muscle, or the gastrocnemei muscles.

OBSERVATIONS

Normal Reflexes

Figs. 2 (knee jerk) and 3 (ankle jerk) show a normal reflex tracing. A indicates the moment that the hammer hit the tendon (less 0·1 msec. for the fly-across), and B indicates the onset of the muscle action potential CD. The initial negative deflection is marked C, and the positive deflection, D. The reflex time is represented by the distance AB, being the time of horizontal travel of the beam before it is deflected vertically to form the initial negative wave of the muscle action potential. In the two figures shown it measured 22 msec. and 42 msec. respectively.

Typical reflex times obtained from an adult 5 ft. 6 in. in height were as follows :—

Knee jerk (rectus femoris muscle)	22 msec.	±1 msec.
Ankle jerk (soleus muscle)	38 msec.	
Biceps jerk (biceps brachii muscle)	15 msec.	
Triceps jerk (outer head triceps muscle)	15 msec.	
Supinator jerk (brachio-radialis muscle)	19 msec.	
Jaw jerk (masseter muscle)	10 msec.	

Factors Influencing Reflex Times

As the reflex time is dependent on many factors, a study was made of the more important of these to see how they might influence the record.

Position of Electrodes in Relation to Muscle.—By placing electrodes at various points over the whole of a muscle, it proved possible to map the muscle in terms of the times of arrival of the muscle-action potential wave. Figs. 4 and 5 illustrate the observations which were made. It can be seen that delays of up to 4 msec. occurred in the reflex time of the knee jerk to different parts of the quadriceps muscle (Fig. 4). The earliest development of negativity takes place near the point of entry of the main nerve trunk, and over a considerable portion of the muscle it begins slightly later than this by the interval required by the terminal branches of the nerve to distribute the exciting nerve impulses throughout the whole muscle. Consequently, when comparing one reflex with its fellow of the other side, the recording electrodes should be placed at symmetrical points, and preferably close to the point of nerve entry. When the recording electrode is over muscle fibres some distance from the motor end-plates, there is an initial positive deflection which reverses to negative as the impulses in the

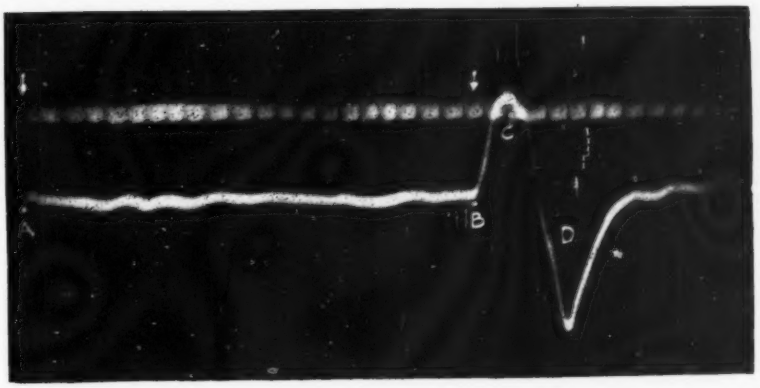

FIG. 2.—Normal reflex (knee jerk). Tracing from rectus femoris muscle. Reflex time : 22 msec. Time tracing in 2 msec. intervals.

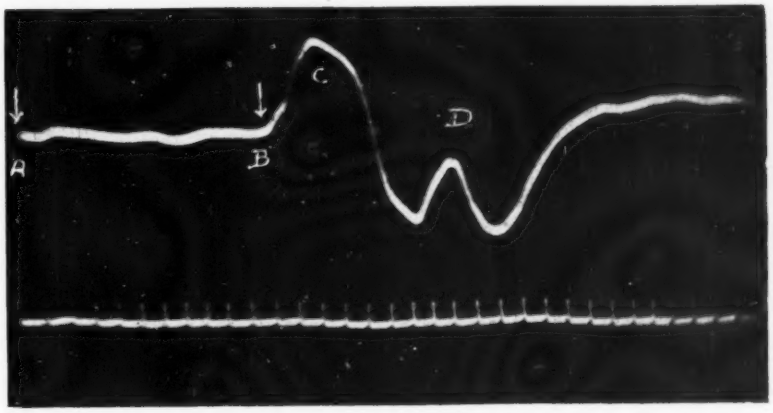

FIG. 3.—Normal reflex (ankle jerk). Tracing from soleus muscle. Reflex time : 42 msec. Time tracing in 2 msec. intervals.

muscle fibre propagate up to the electrode (Eccles and O'Connor, 1939). The recorded potential then has a triphasic configuration. Over the gastrocnemius muscle these triphasic potentials are frequently observed (Fig. 5). Presumably this is attributable to the arrangement of the muscle fibres, since the great majority of the end-plates lie deep within the muscle.

Strength of Blow.—The strength of the blow, provided it was adequate to give a visible response in the muscle, was found to have little bearing upon the reflex time. With very soft taps the reflex time was prolonged, but this was more apparent than real, for the point of onset of the initial negative deflection became more difficult to determine. Provided there was a sharp deflection at the onset of the action potential, reflex times did not vary more than $\pm 0{\cdot}5$ msec.

Reinforcement.—By using reinforcement (locking both hands together and attempting to pull them apart while the tendon is being struck) the only change was an increase in the voltage developed ; the reflex time remained the same. This method was often used with advantage because, with the larger potential developed, the point of onset of the response was sharper and more clearly defined.

TABLE I

REFLEX TIMES FOR ANKLE JERK WITH VARYING DEGREE OF TENSION ON THE TENDO ACHILLIS

Weight Applied (lb.)	Readings* (msec.)	Voltage Response (mv.)	Comment
0	$34{\cdot}5 \pm 0{\cdot}5$	0·05 to 0·3	Voltage response too erratic
½	$34{\cdot}5 \pm 1{\cdot}0$	0·1 to 0·2	Reflex time variable
1	$34{\cdot}5 \pm 0{\cdot}5$	0·1 to 0·2	Consistent results and adopted as standard

* Average of six.

Tension of the Tendon.—Alterations in the tension on the tendon will provoke variations in the muscle voltage, but the reflex time remains fairly constant (Table I). It is therefore advisable to adopt standard postures for the limbs when recording. The knee jerk was always taken with the patient sitting and the legs hanging freely over the edge. For the ankle jerk the patient lay in the prone position with his feet out over the end of the couch, and, by means of a 1 lb. lead weight and pulley, the tension was applied by a cloth band around the region of the metatarsal heads (Fig. 6).

Height of the Patient.—By using comparable points on the rectus femoris muscle in a series of 24 volunteers, both children and adults, a graph (Fig. 7) was constructed correlating the reflex time of the knee jerk and the height of the subject. In this graph, the findings of Whitehorn and Lundholm (1930) are shown for comparison. The graph shows that the reflex time is roughly proportional to the height of the subject.

Sphere of Pick-up of Surface Electrodes.—In order to determine how much the electrical

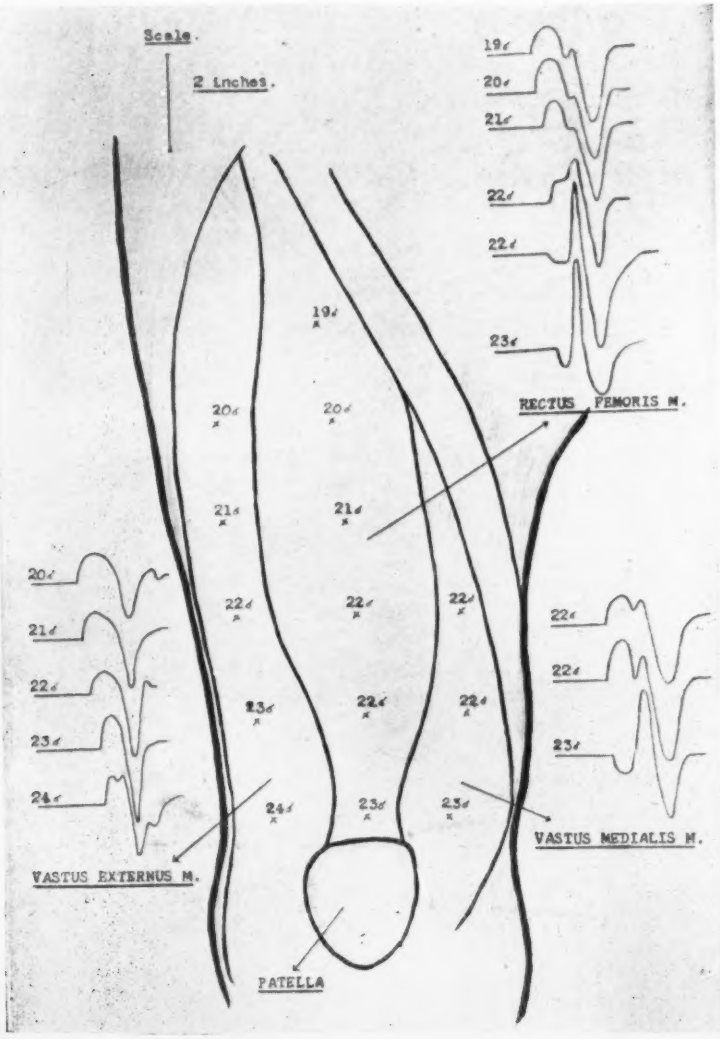

FIG. 4.—Outline drawing of right quadriceps muscle showing at various points the time of arrival of the muscle action potential and response to a blow on the patella tendon. The configuration of the muscle action potential is shown in the three groups of tracings.

record is influenced by voltage changes arising in muscle at a distance from the site of the surface electrode, a comparison was made between the responses obtained with the surface electrode and those obtained with a concentric needle electrode. The sphere of pick-up of the latter has been determined by Weddell, Feinstein, and Pattle (1944) as approximately 2 cm. from the tip. That the surface electrode has a sphere of pick-up which is no greater, at least in the longitudinal axis of the muscle, is suggested by the fact that agreement in reflex times to within fractions of a millisecond was obtained by either method. Therefore a method of recording muscle action potentials by means of surface electrodes is deemed valid.

Speed of Conduction of Impulses through Nerves.—Variations in the speed of conduction in human motor nerve fibres under physiological conditions were investigated because they are a major factor in the conduction time of any tendon jerk. For this purpose, separate experiments involving the ulnar nerve and the hypothenar muscles were devised (Table II). In several normal adults the ulnar nerve was stimulated percutaneously at three points: A, immediately below the anterior axillary fold; B, behind the internal epicondyle of the humerus; and C, at the wrist immediately proximal to the pisiform bone. The muscle recording electrode was placed at a central point over the hypothenar eminence. The time taken between stimulation at each of these points and the appearance of the muscle-action potential was measured. By subtraction the time taken by the nerve impulse over the distances AB and BC was obtained, and the conduction velocity was calculated.

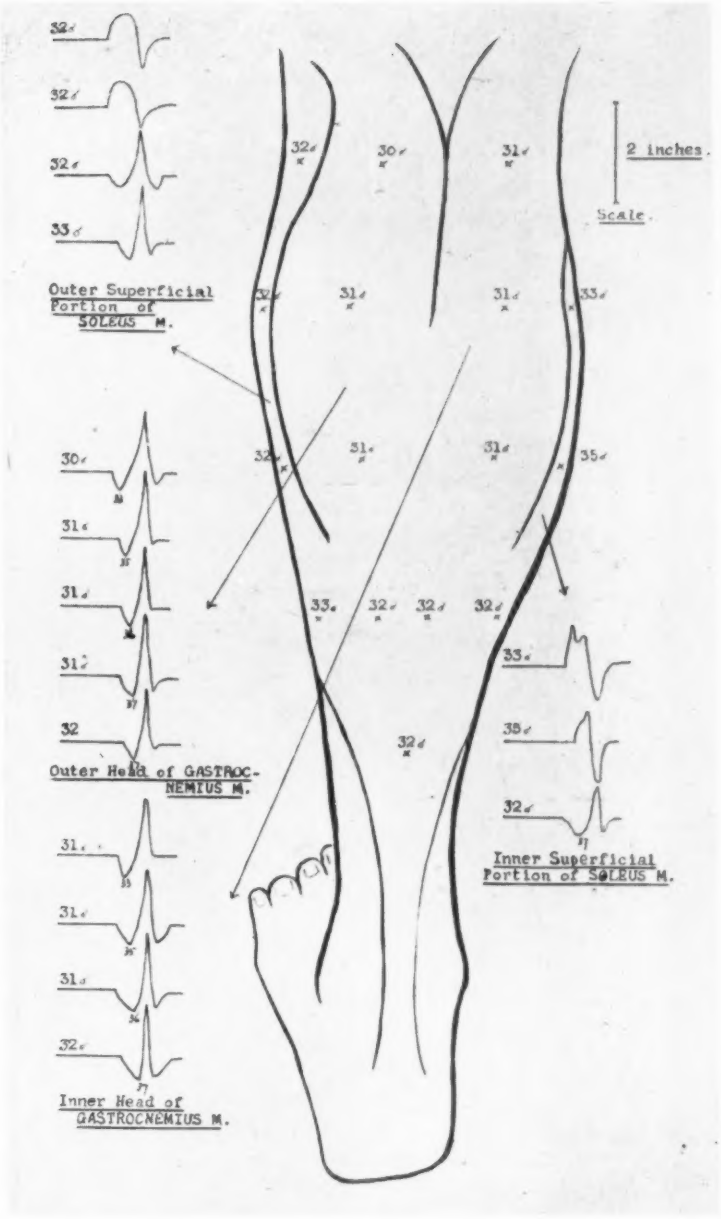
2 inches.
Scale.
Outer Superficial Portion of SOLEUS M.
Outer Head of GASTROCNEMIUS M.
Inner Head of GASTROCNEMIUS M.
Inner Superficial Portion of SOLEUS M.

FIG. 5.—Outline drawing of left soleus and gastrocnemei muscles showing at various points the time of arrival of the muscle action potential in response to a blow on the Achilles tendon. The configuration of the muscle action potential is shown in the four groups of tracings.

It can be seen that in one subject, in whom five separate observations were made at different times, variations in the conduction rate of between 52 and 70 metres per second were observed. These variations were probably accounted for by differing temperatures of the limb, for in Table II(b) the temperature factor was controlled, and when the limb was warmed above the usual level the conduction velocity increased from 63 to 79 metres per second. Presumably the velocity at normal body temperatures is normally between 60 and 70 metres per second, and this was also suggested in another experiment when a length of human nerve (branch of the internal popliteal nerve to the tibialis posticus muscle) obtained from a freshly amputated limb was kept alive for two hours. The maximum speed of conduction recorded under these conditions which were as nearly physiological as possible, was 60 metres per second.

Effect of Pyramidal, and Other Lesions.—From present-day knowledge of the tendon reflexes it would not be expected that lesions of the pyramidal, extra-pyramidal, or cerebellar pathways would

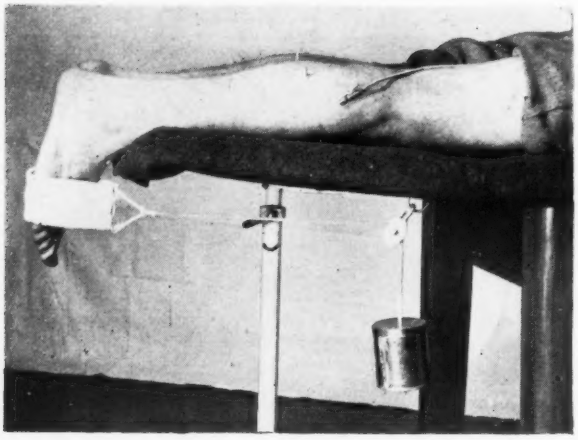

FIG. 6.—The standard method of obtaining tension on the tendo Achillis for eliciting the ankle jerk.

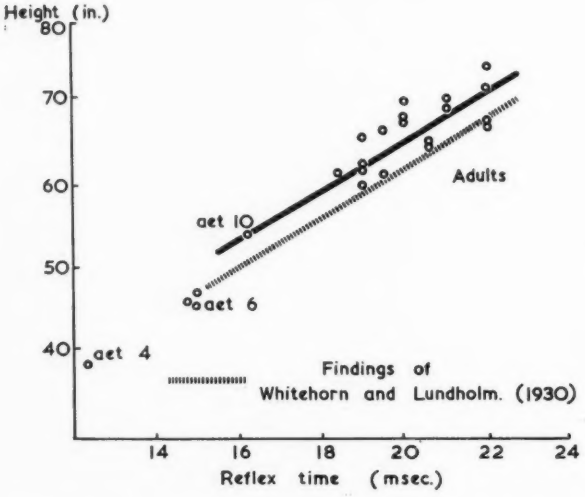

FIG. 7.—Correlation of height and knee jerk reflex time in normal subjects.

appreciably influence the time relations of the reflex. The series of cases presented in Table III supports this view. Similarly, no appreciable alteration in reflex conduction times was noted in patients suffering from a variety of endocrine disorders with metabolic upsets (Table IV).

Voltages Developed.—The voltages developed varied in normal subjects with moderately brisk reflexes; the present apparatus usually registered a negative deflection of approximately 0·3 mv. When the reflexes were exaggerated, as in an upper motor neurone lesion, the voltage obtained by a maximal blow might rise to the vicinity of 1·0 mv., whereas in diminished reflexes the muscle voltage seemed correspondingly less. As a quantitative measure of the reflex response, however, the eye was approximately as sensitive, for the apparatus could not register a response when there was an absent tendon reflex to the naked eye.

TABLE II (A)

STIMULATION OF ULNAR NERVE AND TIME OF ONSET OF ACTION POTENTIAL IN THE HYPOTHENAR MUSCLES

Subject	Length of Ulnar Nerve Measured (cm.)	Time Taken (msec.)	Velocity (metres per sec.)
D.M.	14 (arm)	2·0	70
P.S.	22 (arm)	3·2	69
D.M.	15 (arm)	2·4	63
	27 (forearm)	4·9	55
D.M.	27 (forearm)	5·2	52
D.M.	27 (forearm)	5·1	53
D.M.	27 (forearm)	4·5	60
W.D.	27 (forearm)	4·8	56
A.C.	26 (forearm)	4·9	53

TABLE II (B)

STIMULATION OF ULNAR NERVE AND CONDUCTION VELOCITY UNDER CONTROLLED TEMPERATURE

Subject	Length of Ulnar Nerve* (cm.)	Skin Temperature (°C)	Conduction Velocity (metres per sec.)
D.M.	15	25	63
		35	79

* Arm at room temperature, then incubated for half an hour at 37° C. Ulnar nerve stimulated as in Table IIa.

In Fig. 8 a quantitative comparison has been made between the voltage developed by reflex response and the response obtained by direct stimulation of the nerve root. It should be noted that, although the voltage developed by direct stimulation is very much greater than in the reflex, this was still not a maximal stimulation of the nerve root.

Nerve Root Compression

Conduction Time of Tendon Reflexes.—Having thus shown the constancy of the conduction times in normal subjects, we were in a position to evaluate the effects of unilateral nerve-root compressions, such as sciatica due to the prolapse of the intervertebral disc. Eleven patients were investigated (Table V), seven of whom had purely unilateral signs and symptoms, while the remainder had evidence of bilateral lesions and must therefore be considered separately. All these patients complained of severe, intractable pain which had not yielded to conservative management.

TABLE III

EFFECT OF PYRAMIDAL AND OTHER LESIONS ON REFLEX TIMES

Condition	Patient	Pathology	Reflex	Reflex Times	
				Right (Msec.)	Left (Msec.)
Pyramidal lesions	A	Right hemiplegia	Knee jerk	21	21
			Supinator	19½	19½
			Triceps	14½	15
	B	Right hemiplegia	Ankle jerk	37	37
	C	Right hemiplegia	Supinator	19½	19
	D	Cerebral diplegia	Ankle jerk	32	32
Cerebellar lesions	E	Left acoustic nerve tumour	Knee jerk	21	21
			Ankle jerk	42	42
	F	Right acoustic nerve tumour	Knee jerk	19½	19½
	G	Tumour left cerebellar lobe	Knee jerk	20½	20½
Extrapyramidal lesions ..	H	Post-encephalitic Parkinsonism	Knee jerk	21½	21½
Normal adults as controls ..			Knee jerk	18–23	
			Ankle jerk	30–45	

TABLE IV

EFFECT OF PYRAMIDAL AND OTHER LESIONS ON REFLEX TIMES IN ENDOCRINE DISORDERS WITH METABOLIC UPSETS

Condition	Patient	B.M.R. (%)	Measured Reflex Time (Msec.)	Calculated Reflex Time from Correlation with Height (Msec.)
Thyrotoxicosis	I	+40	Knee jerk 19	20
	J	+55	Knee jerk 22	21
	K	+46	Ankle jerk 36	36
Hypopituitarism	L	−20	Knee jerk 20	21
Fröhlich's syndrome	M	Normal	Knee jerk 19	19

In the group with purely unilateral lesions it was found that five of the seven patients showed delay of 1 to 4 msec. in the reflex time on the affected side. (In four of these there was a compression of the first sacral nerve-root, and in the fifth compression of the fourth lumbar nerve-root.) There remain two cases in this group, patients I and IV, where no delay in reflex time was recorded ; yet from both the clinical investigations and operative findings there is proof that a unilateral lesion existed : in the first instance an L.5 nerve-root, in the second an S.1 nerve-root.

The results from the second group where evidence of bilateral lesions existed, can be analysed as follows : in two instances, patients VIII and XI, clinical evidence of bilateral lesions existed, and the delay in reflex time corresponded to the side giving the more severe symptoms and was in keeping with the operative findings. In the other two cases, patients IX and X, bilateral lesions again existed, but the delay was present on the side which one would have thought, judging from the operative appearances, was now the less compressed. However, in both cases there had been a history of severe pain on the side which was delayed but this pain had since eased ; it may well be that these nerve-roots were damaged at this earlier date.

Considering all these results together, it is evident that of the 11 patients investigated seven showed a delay in reflex time which was in keeping with the clinical and operative findings ; two others showed no delay when unilateral lesions were found to be

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TABLE V

EFFECT OF NERVE-ROOT COMPRESSION ON CONDUCTION TIME OF TENDON REFLEXES

Case No. Clinical Diagnosis : Nerve Root Compressed	Clinical State of Tendon Jerk				Pre-operative Observations of Reflex Times *				Operation Observations of Nerve Root Conduction Times				Nerve Root Pathology Revealed at Operation
	Ankle Jerk		Knee Jerk		Ankle Jerk		Knee Jerk		Nerve Root Stimulated	Muscle Recorded	Time taken between Nerve Root Stimulation and Muscle Response *		
	Right	Left	Right	Left	Right (Msec.)	Left (Msec.)	Right (Msec.)	Left (Msec.)			Right (Msec.)	Left (Msec.)	
I Sciatica L. 5. Left	+	+	+	+	39	39	21	21	L. 5	Gastrocnemius	13·2	14·2	Left root compressed
									S. 1	Gastrocnemius	14·5	14·4	No compression
II Sciatica S. 1. Left	+	±	+	+	37	41	22	22	L. 5	Gastrocnemius	13·0	13·2	No compression
									S. 1	Gastrocnemius	12·6	19·1	Left root compressed
III Sciatica S. 1. Left	+	+	+	+	34	35	18½	18½	L. 5	Soleus	14·9	15·2	No compression
									S. 1	Soleus	17·5	18·5	Left root compressed
IV Sciatica S. 1. Right	±	+	+	+	40	40	22	22	—	—	—	—	Right S. 1 nerve root compressed
V Sciatica S. 1. Left	+	±	+	+	37½	39½	21	21	—	—	—	—	Left S. 1 nerve root compressed
VI Sciatica S. 1. Right	±	+	+	+	44	42	22	22	—	—	—	—	Right S. 1 nerve root compressed
VII Anterior crural neuralgia L. 4. Left	+	+	+	+	37	37	21	23	L. 4	Rectus femoris	8·7	11·5	Left root compressed
VIII Sciatica L. 5. Bilateral Left > right S. 1. Left	+	+	+	+	33	35	20	20	L. 5	Gastrocnemius	16·0	14·9	Both nerve roots compressed
									S. 1	Gastrocnemius	15·4	18·8	Left root compressed
IX Sciatica S. 1. Bilateral	±	+	+	+	37	39	21	21	L. 5	Soleus	15·0	15·1	No compression
									S. 1	Soleus	15·3	15·0	Both roots compressed ; right > left
X Sciatica S. 1. Right > left	+	+	+	+	35	36½	22	22	L. 5	Soleus	15·6	15·8	No compression
									S. 1	Soleus	15·2	15·1	Both roots compressed ; right > left
XI Sciatica S. 1. Right > left	±	+	±	+	40	38½	20½	20½	—	—	—	—	Both nerve roots compressed ; right > left

All the time measurements in this table are an average of the readings obtained from at least six separate tracings taken from the same point on any one muscle.
* Delayed times are underlined.

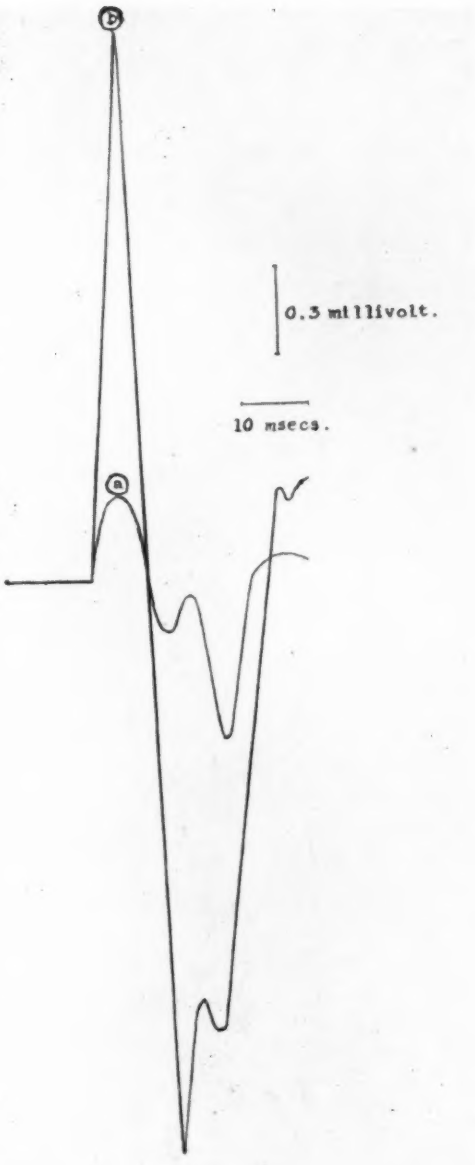

FIG. 8.—Comparison of the voltages developed in the rectus femoris muscle (a) by a blow on the tendon, and (b) by submaximal stimulation of the fourth lumbar nerve root (patient VII).

present by operative investigation, and in the remaining two cases operation revealed bilateral lesions with the more macroscopic nerve-root compression on the side which did not show a delay by the reflex time method.

Further analysis of these cases shows that it is in lesions of the first sacral nerve root that alterations are more consistently obtained. The clinical state of the tendon jerk does not always mirror the delay found in reflex time; there were two instances, patients III and VII, where no visual difference could be detected in the reflexes, and yet delays of 1 and 2 msec. existed, whereas in patient IV there was no delay and yet clinically a marked diminution of the ankle jerk on the affected side. In the two cases where the reflex method gave contradictory results to the clinical and pathological findings bilateral compressions of the first sacral nerve roots were found. Reference will be made again to these two cases, for in neither instance could a delay be demonstrated at operation in the individual nerve roots subserving the ankle jerk.

Conduction Rates Past the Compressed Segment.—In seven of the 11 patients in whom the reflex times had been measured pre-operatively an opportunity was taken at operation to measure the conduction rates in the motor root past the compressed segment. This was done according to the method already described, in which by stimulating the individual nerve root within the theca a recording was made of the time taken by a synchronous volley of nerve impulses to travel from above the site of compression down the nerve to the muscle; this was then compared with the conduction time of the normal nerve roots. It can be seen that in five cases there were delays of from 1·0 msec. to 6·5 msec., in keeping with the pathological findings. In the remaining two cases, both of which had bilateral compression of nerve roots, no delay could be detected when comparing one side with the other; and neither side appears delayed, for the conduction times when compared with controls appear to be within normal limits.

Table VI also shows that there is no correlation between the amount of delay and the clinical assessment of the reflex. Patient III showed the shortest delay of 1·0 msec. and the ankle jerks were equal, but patient VIII, with a delay of 3·4 msec., also had no visible alteration of the reflexes. A useful comparison can also be made between the delay recorded by the reflex method and that obtained by direct nerve root stimulation; patient III showed a 1 msec. delay by both methods, while in all of the others the delay was markedly less when the reflex method was used. Thus in patient II, in whom the direct stimulation method gave a 6·5 msec. delay, the reflex time delay was only 4 msec

Discussion

This study has shown how constant the reflex time is in health and disease, being unaffected in metabolic disturbances, and in lesions of the pyramidal, extrapyramidal, and cerebellar tracts. The fact that a delay frequently occurs in sciatica

All the time measurements in this table are an average of the readings obtained from at least six separate tracings taken from the same point on any one muscle.
* Delayed times are underlined.

on the side of the symptoms must therefore be of significance, even though it does not occur in all cases.

These delays in the reflex time result from the slowing of the passage of nerve impulses through the region of the compressed nerve-root. The slowing of conduction is more marked and more constant when the actual nerve-root affected is investigated than when the appropriate tendon jerk is examined. This is because more than one root enters into the reflex, and as the second and third roots might be normal the delay is less apparent. Tinel (1917), for instance, showed that the knee jerk is not usually abolished unless there is a lesion affecting the third and fourth lumbar segments of the cord or their nerve-roots. Therefore, when the fourth lumbar nerve-root is compressed, the reflex pathway is still unaffected in the third lumbar segment. Again, the ankle jerk is not usually lost after fifth lumbar nerve-root compression, but only after compression of the first sacral nerve-root, for in this case it is the latter nerve-root which is the principal root concerned.

The experimental results show that it is in the unilateral lesions of the first sacral nerve-root that a delay in the ankle jerk reflex time is most constantly found and can be demonstrated even with greater certainty by direct stimulation of the nerve-root above the level of the lesion. The clinical assessment of a diminished tendon reflex does not always run *pari passu* with the delay in the conduction time.

Summary

The reflex time of both the ankle jerk and knee jerk in normal adults has been found to be constant. The application of this method of measuring reflex times to the study of nerve-root compression is described. A longer reflex time has been found on the affected side in patients with lesions which produce unilateral nerve-root compression. Evidence is presented which suggests that in these patients there is a slowing of the speed of nerve-impulse conduction past the compressed segment of nerve-root.

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ARTERIOGRAPHY AND CAROTID ARTERY LIGATION IN INTRACRANIAL ANEURYSM AND VASCULAR MALFORMATION*

BY

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Referring to carotid artery ligation Matas (1909) stated that " the possible occurrence of cerebral disturbance has invested a simple technical procedure with a gravity associated with but few operations ". Statistics (Watson and Silverstone, 1939) compiled from cases in which carotid ligation was done for haemorrhage in the course of operations for advanced malignant neoplasms of the head and neck disclose an extremely high incidence of severe complications and a mortality of about 50%. The statistics however are misleading and do not indicate the results to be expected following carotid ligation for intracranial aneurysms, vascular malformations, and arteriovenous fistulas.

John Abernethy (Garrison, 1913), John Hunter's immediate successor in London, ligated the common carotid artery for haemorrhage in 1798, but his patient died 30 hours later. Fleming (Keevil, 1949), a young surgeon in the Royal Navy, is credited with the first successful ligation of the common carotid artery on October 17, 1803. His patient attempted to commit suicide by cutting his throat while serving on *H.M.S. Tonnant*. Fleming treated the neck wound and his patient was convalescing satisfactorily when eight days later, on October 25, 1803, during a severe paroxysm of coughing the carotid artery burst. Fleming cut down on the common carotid artery below the wound and tied it. The patient made an uneventful recovery.

During the first half of the nineteenth century ligation of the carotid artery was frequent, not only for haemorrhage and peripheral aneurysms but also for epilepsy, psychoses, and trigeminal neuralgia. In 1868 Pilz collected 600 cases of ligature of the common carotid artery with a 43% mortality. In 1902 Horsley (quoted by Beadles, 1907) ligated the right common carotid artery in the neck for an intracranial aneurysm discovered during a craniotomy for a suspected brain tumour. His patient was followed up for five years and was well at that time. Sporadic case reports of carotid ligation for intracranial aneurysm appeared in the literature from then until 1940, when Schorstein reported 60 cases of carotid ligation for intracranial aneurysms of spontaneous origin. Twenty-seven of the cases had previously been reported. The remaining 33 were contributed by members of the Society of British Neurological Surgeons. Rogers in 1947 reported ligation and division of the common carotid artery in seven cases of spontaneous subarachnoid haemorrhage due presumably to leaking aneurysms. Wechsler and Gross in 1948 advocated arteriography and ligation of the common carotid artery in subarachnoid haemorrhage due not only to leaking aneurysms but also in some cases of cerebral vascular malformations.

The introduction of cerebral angiography by Moniz in 1927 and reported fully in 1934 stimulated an interest in intracranial aneurysms and vascular malformations; the number of cases treated in most neurosurgical clinics has greatly increased. There is still, however, considerable controversy regarding the surgical management of these lesions. Dandy (1938), Jaeger (1950), and others advocated the direct intracranial exposure of most intracranial aneurysms and their obliteration either by ligating the neck of the aneurysm, trapping it between two clips, or placing strips of muscle on the aneurysmal wall. Rogers (1947b), and Wechsler and Gross (1948) have employed common carotid ligation in the treatment of intracranial aneurysms of the circle of Willis. The number of cases of cerebral vascular malformations which have been diagnosed has also increased greatly since the advent of cerebral angiography. There is also difference of opinion regarding the treatment of vascular malformations. Excision, radiotherapy, and carotid artery ligation have been advocated. Since 1939 we have carried

* Paper read at a meeting of the American Neurological Association, Atlantic City, June 13, 1950.

Case No.	Sex	Age	First Symptom	Clinical Summary
1. R.G.	F	34	Occipital pain	Headache; stiff neck; L. 3rd nerve palsy int. and ext.; no hemiplegia; mental state normal; fundi normal; C.S.F. negative; no convulsions.
2. L.S.	M	23	Left frontal headache	Headache; stiff neck; eye signs normal; no hemiplegia; lethargic; fundi normal; C.S.F. grossly bloody; no convulsions.
3. M.C.	F	54	Cervical pain	Headache; stiff neck; R. 3rd nerve palsy complete int. and ext.; no hemiplegia; mental state normal; slight blurring of fundi; C.S.F. bloody; no convulsions.
4. J.M.	F	28	Loss of consciousness	Headache; stiff neck; partial L. 3rd nerve palsy; no hemiplegia; normal mental state; fundi normal; C.S.F. xanthochromic; no convulsions.
5. B.B.	F	47	Syncope	Headache; stiff neck; eye signs normal; L. hemiplegia; mental state confused; fundi normal; C.S.F. xanthochromic; convulsions; old C.N.S. lues.
6. L.M.	F	21	R. orbital pain	Headache; no stiff neck; R. exophthalmos and blindness; no hemiplegia; mental state normal; R. optic atrophy; C.S.F. normal; no convulsions.
7. F.N.	F	40	Headache	Headache; stiff neck; eye signs normal; L. hemiparesis; mentally confused and lethargic; fundi normal; C.S.F. bloody; no convulsions; aphasia.
8. J.M.	F	30	L. headache	Headache; stiff neck; partial L. 3rd nerve palsy; no hemiplegia; confused mentally; fundi normal; C.S.F. bloody; no convulsions; anomia.
9. M.K.	F	46	Nocturnal headache	Headache; stiff neck; eye signs normal; no hemiplegia; confused mentally; blurred discs; C.S.F. xanthochromic; no convulsions.
10. M.W.	F (Negro)	23	Occipital pain	Headache; stiff neck; eye signs normal; L. hemiplegia; stupor; fundi normal; C.S.F. bloody; convulsions; bilateral Babinski signs.
11. J.M.	F	51	Pain R. eye	Headache; no stiff neck; complete R. 3rd nerve paralysis; no hemiplegia; *Witzelsucht*; fundi normal; C.S.F. bloody; no convulsions; L. hyperreflexia.
12. M.F.	F	46	Headache	Headache; no stiff neck; L. pupil greater than R.; no hemiplegia; mental state normal; fundi normal; C.S.F. xanthochromic; no convulsions.
13. S.R.	F	32	Unconsciousness	Headache; stiff neck; both pupils fixed and dilated; L. hemiplegia; mental confusion and coma; normal fundi; C.S.F. bloody; no convulsions; bilateral Babinski signs.
14. L.B.	F	58	Convulsions	Headache; no stiff neck; optic atrophy; no hemiplegia; mentally confused; C.S.F. normal; frequent convulsions; incontinence.
15. P.S.	F	60	R. ptosis	Headache; no stiff neck; complete R. 3rd nerve palsy; no hemiplegia; mentally depressed; R. optic atrophy; C.S.F. normal; no convulsions; R. corneal reflex absent.
16. C.B.	F	46	R. eye pain	Headache; no stiff neck; complete R. 3rd nerve palsy; no hemiplegia; normal mentally; fundi normal; C.S.F. normal; no convulsions.
17. A.S.	M	48	Loss of consciousness	Headache; stiff neck; complete L. 3rd nerve palsy; mentally confused and lethargic; blurred discs; C.S.F. xanthochromic (pressure 430); convulsions; R. facial, central.

B.P.	Arteriogram	Site	Treatment	Result
130/80	Positive	Post.-commun.	Com. carotid ligated	Ptosis improved. No headache. Has remained well for 4 years
128/70	Positive	Bifurcation of anterior and mid-cerebral	Ligation and division L. com. carotid	Improved. No follow-up
180/95	Positive	Post.-commun.	Ligation R. com. carotid	3rd nerve paralysis cleared up. Remained well for over 2 years (last follow-up)
115/65	Positive	At origin L. mid. cerebral (Fig. 2)	Ligation and division L. com. carotid	Symptom-free and working 2 years later
148/100	Positive	R. mid. cerebral	Ligation and division R. com. carotid	1 year follow-up. No symptoms; very slight L. hemiparesis
—	Positive	Junction carotid and ophthalmic	Ligation com. carotid; craniotomy with clip on neck of aneurysm	Has remained well though blind in R. eye. 8 year follow-up
135/80	Positive	L. middle cerebral	Ligation L. com. carotid	—
108/70	Not done	—	Ligation and division L. com. carotid	Symptom-free 2 years
150/100	Positive	R. middle cerebral	Ligation and division com. carotid	No symptoms 3 months later
—	Positive	R. middle cerebral	Ligation R. com. carotid and craniotomy with clip on neck of aneurysm	Died 4 weeks later. No necropsy
130/70	Positive	Post.-commun. at carotid	Ligation and division R. com. carotid	Marked improvement. Ptosis improved. Recent case (3.7.50)
120/80	Positive	R. middle cerebral	Ligation R. com. carotid	No symptoms at time of discharge
80/50	Positive	Post.-commun. at junction with carotid	Ligation R. com. carotid	Died 9 hours later
—	Positive	L. anterior fossa (Fig. 1)	Ligation L. com. carotid; bi-frontal craniotomy	Improved for 10 months after ligation. Died 10 days after craniotomy
220/140	Not done	R. middle fossa	Craniotomy and ligation R. com. and external carotid	Ptosis cleared up; 2 year follow-up
140/70	Unsatisfactory	?	Ligation R. com. carotid	Immediate relief of pain; 3rd nerve palsy improved
130/70	Positive	L. internal carotid	Ligation and division L. com. carotid	6 hours later R. hemiplegia and aphasia 5 months later much improved

out a more or less uniform policy, employing carotid artery ligation in most cases of subarachnoid bleeding whether due to a leaking aneurysm or rupture of a vascular malformation. In nearly all cases the lesion was verified by arteriography and, in a few, by direct intracranial exposure. Our experience includes traumatic and spontaneous intracranial arteriovenous fistulas, in which the problem of treatment is somewhat similar.

Aneurysms of the Circle of Willis

Our material consists of 17 cases (Table I). All were treated by carotid artery ligation, and in four cases the lesion was also exposed intracranially. In two cases the aneurysm had a neck small enough to permit ligation with a silver clip. In the early cases, after an arteriogram, the common carotid artery was merely ligated in continuity with a silk ligature after a preliminary temporary occlusion for ten minutes or longer had been well tolerated. In seven cases the common carotid was divided after double ligation and the cut ends were transfixed.

In considering ligation of the carotid artery several questions must be answered : What are the dangers of carotid ligation ? If ligation is decided upon, shall it be the common or internal carotid ? Should one merely ligate, or doubly ligate and divide ? Finally, how effective is ligation in the treatment of intracranial aneurysms ?

Although there are many variations in the circle of Willis, it is incomplete in less than 10% of specimens examined (Padget, 1944). Variations in the size of the vessels are more common. In a series of adult brains studied by Fetterman and Moran (1941), the posterior communicating arteries were " threadlike " in 20% of 200 cases. The anterior communicating artery may be duplicated in some cases : in others it is absent, the circle being completed by fusion of the anterior cerebral arteries. The arteries of the circle of Willis serve as anastomotic channels for an alternate course of blood flow when obstruction of one of the main vessels occurs. The circle is not an equalizer or distributing station (Rogers, 1947a). Sweet and Bennett (1948) showed that in man the systolic pressure falls to 50% and the pulse pressure to 25% of their original levels in the distal portion of the internal carotid artery when the vessel is occluded in the neck. They also found that significant retrograde flow from the external to the internal carotid artery usually does not occur when the common carotid alone is occluded. This refutes the often repeated statement in the literature regarding collateral circulation through the external carotid artery when the common carotid is ligated.

The dangers of carotid artery ligation may be divided into the early and the late. The immediate complications result from cerebral ischaemia. Toleration of digital compression of the common or internal carotid arteries in the neck (Matas test) for a period of ten minutes has been taken to indicate an adequate collateral circulation, but Sweet and Bennett have shown that this test is grossly unreliable.

We have carried out nearly all of our carotid artery ligations under local anaesthesia. Before ligation the artery is always occluded temporarily for at least ten minutes when the patient is carefully observed for the development of new neurological disturbances. In addition, we now take an electroencephalogram during temporary occlusion of the common and internal carotid arteries when the vessels are directly exposed under local anaesthesia. Our results will be reported later. In 30 carotid artery ligations, 28 of the common and two of the internal carotid, there were no immediate complications. Delayed complications occurred in four of our patients : one in a case of aneurysm of the internal carotid, one of traumatic arteriovenous fistula, one of spontaneous arteriovenous fistula, and one of vascular malformation. In the patient with an aneurysm of the intracranial portion of the internal carotid artery the ligation resulted in some permanent neurological disturbance.

Case Report

The patient was a man aged 48 (Case 17). Several years previously he suddenly lost consciousness, and a lumbar puncture showed a bloody cerebrospinal fluid. He gradually improved, though he had diplopia for several weeks. He remained well until three weeks before his second hospital admission when he suddenly developed headache, vomiting, and ptosis of the left upper lid. He had a stiff neck at this time, and it seemed quite evident that he had a leaking intracranial aneurysm. He was confused and complained of severe headache. The fundi showed blurred disc margins. There was a complete internal and external left third nerve paralysis and a right central facial weakness. On the third hospital day he had a severe generalized convulsion. Four days later an arteriogram was taken under local anaesthesia. Although the films were not entirely satisfactory, they indicated an aneurysm of the left internal carotid artery. The common carotid artery was occluded for ten minutes with a tape. The patient had been restless and uncooperative throughout the entire procedure, but as no new neurological abnormalities developed the common carotid artery was doubly ligated and cut between the ligatures. About six hours later he developed a right hemiparesis and aphasia. Gradual improvement began in a few days. Four months later he had slight residual weakness of the right hand and some anomia, but was in excellent

general health, free of headache, and the left ptosis was improving.

Schorstein (1940) discussed the theories regarding delayed complications resulting from carotid artery ligation. The embolic theory has been the one most often quoted. It assumes that a thrombus forms at the site of ligature and that detached pieces of the thrombus lodge in the branches of the circle of Willis. There has been very little pathological evidence to support this theory. Another theory assumes that a thrombus extending upwards forms in the ligatured vessel. Spasm of the carotid artery and its branches distal to the site of ligature has been advanced as a possible cause of immediate and delayed complications. While this theory is plausible, there has been no convincing experimental evidence to substantiate it.

There is considerable controversy in the literature regarding which vessel to ligate. Most authors state that ligation of the internal carotid artery is much more hazardous than ligation of the common carotid artery. The assumption is that occlusion of the common carotid reduces blood flow through the internal carotid by only about 50% because of retrograde collateral circulation through the external carotid, but the work of Sweet and Bennett (1948) contradicts this contention. Nevertheless, the collected experiences in the reported cases bear out the impression that ligation of the internal carotid is much more likely to result in cerebral disturbances or death. The explanation for this is not entirely clear. Schorstein believes that cerebral disturbances after carotid ligation are most likely due to failure of the systemic circulation. The high incidence of complications when the carotid artery is ligated for haemorrhage in the course of an operation for a tumour in the neck, or when ligation is done in old or debilitated individuals, supports this view.

The advantages of dividing the occluded vessel between ligatures are probably more theoretical than real. Rogers (1947b) believes that by dividing the occluded vessel the accompanying sympathetic nerves are also severed and vasospasm in the distal arterial segment and its branches is avoided. Embolism is less likely after division of an occluded artery, since the pumping action of the pulse beat at the ligature site is avoided and the free distal arterial segment shuts down on the clot.

In 17 cases in which carotid ligation was used in the treatment of intracranial aneurysms of the circle of Willis there were three deaths. In Case 10 (previously reported ; Wechsler and Gross, 1948) the patient was critically ill. She had had two convulsions, a left hemiplegia with forced deviation of the eyes to the right, and a grossly bloody cerebrospinal fluid under a pressure of 300 mm. Arteriography showed a berry aneurysm springing from the middle cerebral artery near its junction with the internal carotid artery. The right common carotid artery was ligated in the neck. Although spinal puncture showed no evidence of fresh bleeding the patient continued in stupor. Four days later an intracranial approach disclosed the aneurysm to have a neck small enough to permit the application of a silver clip. The patient slowly improved for almost one month when she suddenly died. Necropsy was not permitted so we are at a loss to explain her death. The second patient (Case 13) was moribund at the time of arteriography and carotid artery ligation, and she died nine hours later. The third patient (Case 14) had a huge subfrontal mass which, from the history and pneumoencephalogram, was thought to be a tumour. Bifrontal exploration showed a large midline aneurysm extending more to the left (Fig. 1). It was at least 3 cm. in diameter. Arteriography and left common carotid ligation were followed by cessation of her previous seizures, but her mental condition deteriorated. Ten months later the old craniotomy wound was reopened and the aneurysm was wired. She failed to improve and died 11 days later.

Of the 14 patients who were discharged from the hospital improved, ten had bloody or xanthochromic cerebrospinal fluid on admission to the hospital. Of these, follow-ups from three months to over two years are available in seven, and they are all well or improving. We first saw one patient (Case 1) about one year after her first attack of subarachnoid haemorrhage. She complained of head pain and had a complete left oculomotor nerve paralysis. Following arteriography and ligation the head pain disappeared and the eye signs cleared up. She has remained well and active for over four years. In every case where the third cranial nerve was involved there was either improvement or complete restoration of function. We do not know of any patient who has had subarachnoid bleeding subsequent to carotid ligation for intracranial aneurysm. Four patients who were improved at the time of discharge from the hospital failed to report to the follow-up clinic (Cases 2, 7, 12, and 16).

In Case 8 carotid ligation was probably a life-saving measure. This patient, a 30 -year-old woman, had a sudden onset of vomiting and loss of consciousness for 15 minutes. Four hours later she had severe left-sided head pain. She was confused. The headache, nausea, and vomiting continued for several days. She had neck rigidity and a bloody spinal fluid. She improved for a few days and then began to have attacks of anomia and numbness of the right hand. She suddenly developed excruci-

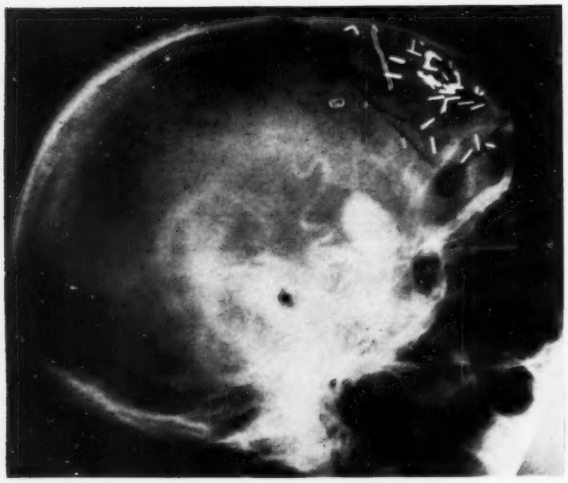

FIG. 1

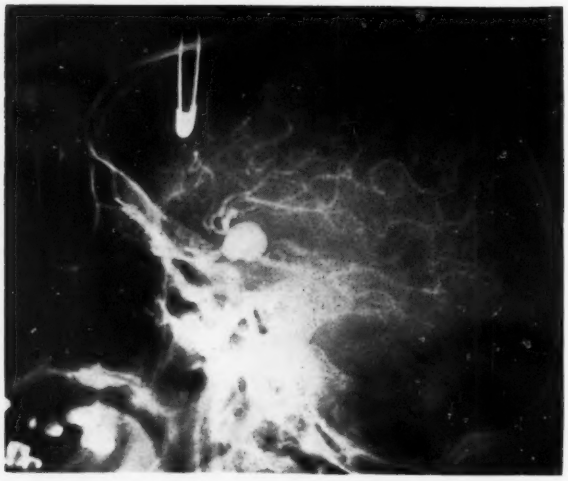

FIG. 2

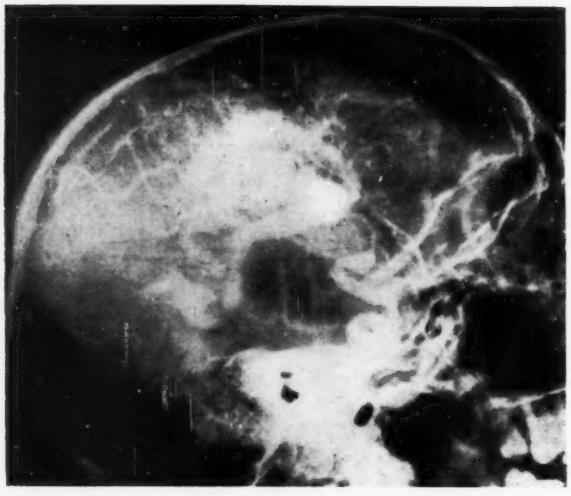

FIG. 3

ating left-sided head pain, and dilatation of the left pupil and left ptosis, and the nuchal rigidity increased. At this time the patient appeared critically ill. The left common carotid artery was doubly ligated and divided. One hour later she was free of headache. She improved rapidly and has remained well for two years.

The ocular signs in aneurysms of the circle of Willis have received a great deal of attention (Walsh and King, 1942). Eye pain associated with ptosis and dilatation of the ipsilateral pupil should lead to a suspicion of an aneurysm of the anterior portion of the circle of Willis. If, in addition, there is evidence of subarachnoid bleeding in the cerebrospinal fluid the diagnosis of aneurysm is almost certain. Complete paralysis, both internal and external, of the oculomotor nerve was present in six of our 17 patients. One patient (Case 8) developed slight ptosis and dilatation of the ipsilateral pupil while in the hospital. This cleared up shortly after common carotid artery ligation. In Case 4 ptosis and dilatation of the pupil also developed during observation. The arteriogram showed an aneurysm at the origin of the middle cerebral artery (Fig. 2). The ocular palsy persisted for two months. When the patient was seen two years later there was no longer any sign of oculomotor weakness.

In 12 of our patients the cerebrospinal fluid was either bloody or xanthochromic. There was a report of a bloody fluid from a recent previous hospital admission in Case 1, although her cerebrospinal fluid was clear and colourless at the time of carotid artery ligation. She applied for treatment because of the ptosis and eye pain.

No unusual reactions to arteriography with 35% diodrast were observed in any of our patients who had bloody or xanthochromic cerebrospinal fluids. Either common carotid artery ligation or ligation and division was done as soon as the wet *x*-ray films were read. The youngest patient in this series was 21, the oldest 60. The average age was 40·5 years. There were only two males in this series. The higher incidence of intracranial aneurysms in females is not peculiar to our series. In cases reported from other clinics aneurysms were also found to occur with greater frequency in females. In Hamby's (1948) series of 130 patients with subarachnoid haemorrhage of presumed aneurysmal origin there were 75 women and 55 men. Eight of

FIG. 1.—Large aneurysm in left anterior fossa (Case 14).

FIG. 2.—Aneurysm of middle cerebral artery (Case 12).

FIG. 3.—Arteriogram, *x*-ray therapy, showing vascular malformation (Case 18).

13 intracranial aneurysms proved at necropsy by Dial and Maurer (1937) occurred in women.

Vascular Malformations

Until the recent widespread use of cerebral angiography, vascular malformations of the brain were rarely reported (Wechsler and Gross, 1948). In their monograph published in 1928 Cushing and Bailey reported 16 cases, an incidence of slightly over 1% of their verified intracranial tumours. Although in recent years numerous references to these lesions have appeared, opinion regarding their treatment has not yet crystallized. There has been much difference of opinion also as to whether cerebral vascular malformations should be classified with neoplasms of the brain, with the congenital anomalies or with the hamartomas (tumour-like anomalies). Olivecrona and Riives (1948) recently reported their experiences with 60 cases of " arteriovenous aneurysms of the brain ", their term for the lesion under discussion. They advocate the radical removal of vascular malformations. In 43 patients so treated there were four deaths.

Our own material consists of nine cases : five women and four men (Table II). The youngest was 17 when first seen by us, the oldest 56. All but two had had subarachnoid bleeding sometime during the course of their illness and five had bloody or xanthochromic cerebrospinal fluid during their current hospital admission. One patient (Case 20) had had an attack of subarachnoid bleeding eight years previously. This was the first evidence of his abnormality. Except for occasional headache he remained well for seven years when he began to have petit mal attacks. About one year later he had a grand mal seizure. An angiogram done at that time revealed an extensive vascular malformation in the left frontal area. His cerebrospinal fluid was normal during his hospital stay. Case 22 and Case 24 had no evidence of subarachnoid bleeding, and their cerebrospinal fluids were clear and colourless during their periods of hospital observation.

Convulsions were present in seven of our patients. Three patients were admitted to the hospital for investigation because of seizures. Arteriography was done in eight patients. In Case 22 an extensive vascular malformation was discovered after a bone flap had been elevated for a presumed brain tumour.

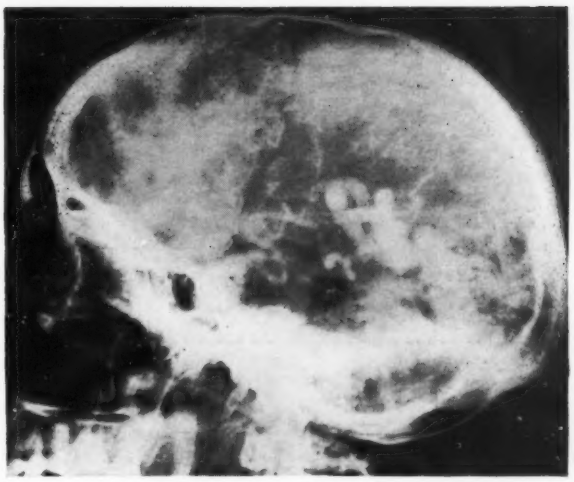

FIG. 4

FIG. 5

FIG. 6

FIG. 4.—Vascular malformation in parietal area (Case 21).

FIG. 5.—Arteriogram, after craniotomy, showing vascular malformation (Case 24).

FIG. 6.—Traumatic arteriovenous fistula (Case 28).

TABLE II. VASCU

Case No.	Sex	Age	First Symptom	Clinical Summary
18. L.K.	F	45	Frontal headache	Headache ; stiff neck ; at least 10 previous attacks ; stupor ; convulsions ; R. Babinski sign and papilloedema ; no brui C.S.F. bloody (pressure 240)
19. S.C.	F	32	Vomiting	Headache ; stiff neck ; at least 5 previous attacks ; drows convulsions ; R. hemiplegia and anomia ; no bruit ; C.S. bloody (pressure 120)
20. E.H.	M	32	Nausea	Headache ; no stiff neck ; 1 previous attack ; mental state norma convulsions ; no bruit ; C.S.F. normal (pressure 210)
21. S.C.	F	30	Vomiting and nausea	Headache ; stiff neck ; no previous attacks ; comatose ; co vulsions ; no bruit ; C.S.F. bloody (pressure 180)
22. S.L.	M	56	Weakness L. hand	Headache ; no stiff neck ; onset 25 years previously ; ment state normal ; convulsions ; L. hemiparesis ; bruit ; C.S. clear and colourless (pressure 280)
23. S.G.	M	17	Weakness L. lower extremity	Headache ; no stiff neck ; 2 previous attacks ; stupor ; co vulsions ; L. hemiparesis ; bruit ; C.S.F. xanthochrom (pressure 320)
24. G.S.	M	42	Jacksonian seizures L. hand	No headache ; no stiff neck ; onset 8 years previously ; ment state normal ; convulsions ; diminished position sense L. han bruit ; C.S.F. clear and colourless (pressure 135)
25. B.S.	F	40	Pain R. eye	Headache ; no stiff neck ; no previous attacks ; confused a apathetic ; no convulsions ; L. hemiparesis and papilloedem no bruit ; C.S.F. xanthochromic (pressure 120)
26. B.O.	F	26	Headache	Headache ; no stiff neck ; attack 2 years previously ; unconsciou convulsions ; bilateral Babinski signs ; no bruit ; C.S. bloody

TABLE III

Case No.	Sex	Age	Aetiology	Duration	Clinical Summary
27. K.P.	F	70	Spontaneous	4 months	Headache ; bruit ; partial R. 3rd nerve palsy ; modera pulsating exophthalmos ; venous engorgement R. fund
28. J.L.	F	42	Trauma	6 months	No headache ; bruit ; slight L. 3rd nerve palsy ; slig non-pulsating exophthalmus ; venous engorgement fundus
29 H.P.	M	22	Trauma	10 months	Headache ; bruit ; normal eye signs ; no exophthalmos normal fundi
30 C.L.	F	30	Trauma	6 weeks	Headache ; bruit ; partial L. 3rd nerve palsy ; modera pulsating exophthalmos ; L. disc blurred and veno engorgement

MALFORMATIONS

B.P.	Arteriogram	Site	Treatment	Result
140/90	Positive (Fig. 3)	R. cerebral	Radiotherapy (1946) without benefit. 1948 R. com. carotid ligated and divided	Follow-up 18 months. No further attacks subarachnoid bleeding which had been recurrent since age 8 years
—	Positive	L. frontal	Ligation L. com. carotid	3 year follow-up. No further bleeding
106/56	Positive	L. frontal	Ligation L. internal carotid	R. hemiparesis and anomia 10 hours later lasting 24 hours. Recent case
120/70	Positive (Fig. 4)	R. parietal	Ligation R. com. carotid	3 year follow-up ; occasional petit mal seizure
140/95	Not done	R. frontal	R. frontal craniotomy. R. com. carotid ligated	2 year follow-up : improved. Extensive R. vascular malformation
130/90	Positive	L. fronto-temporal	Decompression. Radiotherapy. Ligation L. com. carotid artery	10 year follow-up. Continues to have convulsions
120/70	Positive (Fig. 5)	R. fronto-parietal	Craniotomy : 2 weeks later ligation and division R. com. carotid	Improved at time of discharge
160/90	Positive	R. post-parietal	Ligation R. com. carotid	3 year follow-up ; remains well
100/62	Positive	R. temporal	Ligation and division R. com. carotid	Recent case (18.3.50)

ARTERIOVENOUS FISTULAS

Arteriogram	Treatment	Result	Remarks
Not done	R. com. carotid ligated and divided	Excellent. 1 year follow-up	2 weeks after ligation L. hemiparesis lasting a few days
Positive (Fig. 6)	L. com. carotid ligated	Improved for 4 years	Recurrence of ptosis for 1 week 4 years later, but improved after 10 days. Has remained well for 5 years since
Positive	R. com. carotid ligated	Immediate relief of symptoms. No follow-up	—
Not done	L. com. carotid ligated	Excellent. Bruit and eye signs recovered	R. brachial monoplegia developed 6 hours later, and lasted 24 hours

This patient had had symptoms for at least 25 years. In retrospect, the correct diagnosis might have been made pre-operatively. A bruit was heard in three of our patients.

In five patients the common carotid artery was ligated; in three the common carotid was ligated and divided between ligatures; in one patient the internal carotid artery was ligated. Case 18 had had many episodes of subarachnoid bleeding starting in early life. An arteriogram was done in 1946. This was followed by high voltage *x*-ray therapy. In spite of this the patient had recurrence of her subarachnoid bleeding and she was re-admitted in 1948 in stupor. The cerebrospinal fluid was bloody. The arteriogram was repeated, again demonstrating the vascular malformation. Its appearance had not been altered by *x*-ray therapy. During this admission the right common carotid artery was ligated and divided. There have been no episodes of subarachnoid bleeding since, now 18 months. Case 23 had had symptoms of neurological disorder since the age of 3. At the age of 17 he had subarachnoid bleeding and was in stupor. An arteriogram demonstrated the vascular malformation. Decompression was done, and radiotherapy given. He improved but continued to have seizures. A few years later the left common carotid artery was ligated but his seizures continued. He has had no further subarachnoid bleeding but the seizures have persisted.

Uniformly good results were obtained in four cases of carotid-cavernous sinus fistulas treated by ligating the common carotid artery in two cases and by doubly ligating and dividing the common carotid in the other two (Table III). Three of the carotid-cavernous fistulas were of traumatic origin; the fourth occurred spontaneously in a 70-year-old arteriosclerotic woman. An intracranial bruit was present in all four patients. In Case 29 the patient complained of headache and head noises. For several weeks he had been treated in another hospital for a psychoneurosis. Following arteriography his common carotid artery was ligated and his symptoms disappeared at once.

The operative mortality and morbidity of ligation of the common carotid artery for aneurysms and vascular malformations compare favourably with that reported following intracranial procedures. The late results, as far as they have gone, apparently are as good. More years of observation will be necessary to provide a final answer. Should follow-up studies by other observers substantiate our observations and results, the simplicity of the carotid ligation should weigh heavily in its favour.

Summary

The results of ligation of the common carotid artery in the neck in 30 cases have been presented. There were 17 aneurysms of the circle of Willis, nine vascular malformations of the hemispheres, and four carotid-cavernous sinus fistulas.

In the malformation group there was no death; one patient developed a hemiparesis. In no case has bleeding recurred after operation. Two patients continued to have convulsions.

In the aneurysm group there was one death nine hours after ligation. The other deaths in this group followed craniotomy, one after ten days and one after four weeks. There has been no recurrence of bleeding. There was one post-ligation hemiplegia with aphasia.

The mortality, morbidity, and results of this method of treatment compare favourably with other methods advocated.

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DISABILITY CAUSED BY BRAIN WOUNDS*

A REVIEW OF 1,166 CASES

BY

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This paper is based on a follow-up study which has continued throughout and since the late war. The study centres around the work done by many specialists at the Military Hospital for Head Injuries, Oxford, and with the mobile neurosurgical units in different theatres of war. The Medical Research Council has assisted throughout in providing for the preservation and copying of case records, and since the war, with aid from the Nuffield Provincial Hospitals Trust, it has been possible to organize a small Head Injury Advice Bureau which aims at providing a competent service to which the pensioner with a brain wound can turn for advice or help. At the same time, this bureau provides an admirable organization for scientific follow-up purposes. The staff consists of an almoner, secretary, psychologist, and any neurologists who may be available. The combination of social welfare and follow-up research studies seems to operate to the mutual advantage of both.

The main purposes of this research are concerned with the ever-stimulating problems regarding the effect of lesions of different areas of the brain, and also with the problems of rehabilitation which the cases present. I shall not, however, describe these special studies, but will rather attempt to give a broad picture of the effects of brain wounds.

Thanks to the helpful cooperation of Ministry of Pensions administrators we have been able to re-examine a good proportion of the cases many years after wounding. Others have been kept in touch with by questionnaire, letter, welfare officer visits, and other means. The features of each case have been transferred to a paramount card (Fig. 1, p. 36) designed to facilitate analysis.

The cases considered were all of men who reached this country alive. It was after the invasion of Normandy that most of the injuries occurred and the wounded often reached the hospital at Oxford by air within one or two days of wounding. A proportion therefore of desperately ill cases arrived in this way, a fact which influenced the early death rate seen in Table I. The main feature of this table, however, is the amazingly low incidence of delayed deaths—a remarkable testimony to the work of many neurosurgeons, and to antibiotics. As to the causes of late death, meningitis and status epilepticus are the most important.

TABLE I

ANALYSIS OF 78 DEATHS OUT OF 1,166 CASES FOLLOWED UP FOR FIVE YEARS

Deaths due to head injury	71 (6%)
Interval after wounding :	
within 1 week	23
1 week to 1 month ..	27
1–2 months	9
over 2 months	12
Deaths from other causes	5
Suicide	2

It is customary to separate wounds which penetrate the dura mater, " penetrators ", from those which cause damage to scalp and skull without dural laceration. This separation is shown in Table II. As will be seen later, the brain is usually

TABLE II

PROPORTION OF 1,088 SURVIVING CASES WITH ADDITIONAL WOUNDS

	Total Surviving Cases	With Additional Wounds
Wounds of scalp and skull, dura intact	268 cases	55 cases (20%)
Wounds penetrating dura and brain	820 cases	254 cases (31%)
Total	1,088 cases	309 cases (28%)

* Paper read to the Edinburgh Medico-Chirurgical Society on December 6, 1950.

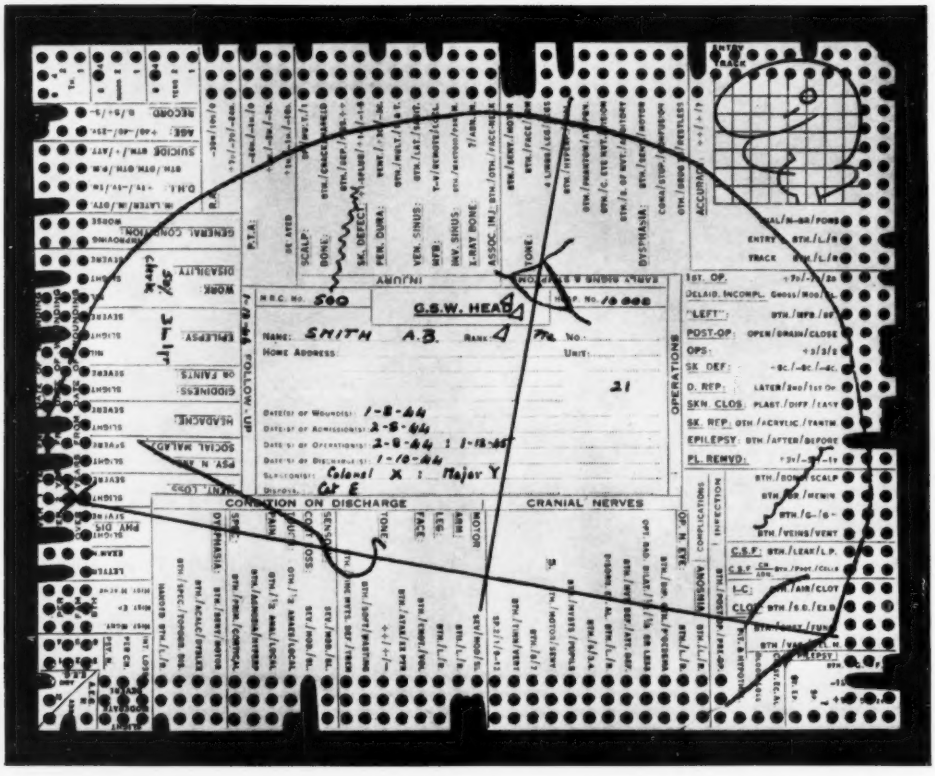

FIG. 1.—Photograph to illustrate the use of the "paramount" card* designed for analysis of these cases. A tracing of the patient's skull radiograph is superimposed.

* Printed by the Copeland-Chatterson Co. Ltd., Stroud, Glos.

injured focally in both types of injury, but the risk of infection is of course much reduced when the dura mater is intact. Table II also demonstrates the high incidence of multiple wounds even in a series of cases selected largely in the acute stage for transfer to a neurosurgical unit.

Early Focal Signs

In the late war most of the cases of head wound which reached hospital alive had been hit by small fragments of high explosive shells (scalp wound of brain, skull or scalp). These metal fragments on striking the head either lodge in the skull, glance away, or cut into the brain. In either case a small shower of bone fragments is often projected into the brain from the point of impact. Many of the resulting lesions are remarkably self-limited and provide unique material for the study of focal brain lesions. This is especially evident when, as often happens, the wounds cause little or no cerebral concussion, so that the duration of post-traumatic amnesia is very short, or indeed there is often no disturbance of consciousness (Table III). This is in striking contrast to the ordinary cases of accidental head injury (Symonds and Russell, 1943) where a period of amnesia is found in all except the slightest injuries. The gun-shot wound cases tend to have either a very short or a long amnesia, whereas in the "accidental" injuries all amnesic groups are well represented except the shortest.

In contrast, however, to the absence of amnesia in many cases, the incidence of gross focal signs immediately after wounding is surprisingly high in this series, even in cases without dural penetration (Table IV). It is of course likely that the occurrence of gross focal signs increased the liability for the case to be evacuated to a special centre. Never-

TABLE III

COMPARISON BETWEEN DURATION OF POST-TRAUMATIC AMNESIA IN SHELL WOUNDS OF THE HEAD AND OF ACCIDENTAL HEAD INJURY

	Duration of Post-traumatic Amnesia (Hours)					
	Nil	−1	1–24	>24	?	Total cases
Shell wound of brain	216	172	57	320	55	820
Shell wound of skull and scalp	123	68	23	36	18	268
"Accidental" head injury (Symonds and Russell, 1943)..	28	75	65	69	—	237

TABLE IV

INCIDENCE OF EARLY FOCAL SIGNS (SENSORI-MOTOR, VISUAL, OR APHASIC) IN 884 CASES

	Total	Cases with Early Focal Signs
Wounds of skull and scalp	191	129 (68%)
Wounds of brain ..	693	517 (75%)*

* Of remaining 176 cases, 152 were frontal wounds.

theless, it seems evident that wounds to all parts of the parietal, temporal, and occipital lobe are very likely to cause focal symptoms, temporary or permanent, such as paralysis, aphasia or partial blindness. As is seen in Table IV, 75% of penetrators had early focal signs. Of the remaining 176 cases, 152 were frontal wounds. These focal disorders are often transient and may be strictly localized. For example, a small mid-Rolandic wound causes paralysis of the opposite arm only, while the small parasagittal wounds of the same area lead to immediate paralysis of one or both legs.

Many students of brain function have considered the effects of trauma to be too uncertain for such cases to be used in the detailed study of focal lesions. My experience of this series, however, has led me to consider that among the cases can be distinguished a number of small wounds which provide excellent material for the study of brain function. These cases are distinguished by studying details of the wound, the operation, the early focal signs, and the permanent disability.

The very high incidence of *early* focal signs in brain wounds seems to depend partly on the spread of a shock effect from the site of wounding. Tables V and VI compare the incidence of early signs with

TABLE V

ANALYSIS OF EARLY AND PERMANENT SENSORI-MOTOR DISORDERS IN 370 OF 693 CASES WITH PENETRATING BRAIN WOUNDS

	Early	Permanent (excluding Slight)
Affecting one arm and/or face	107	43
„ arm and leg	192	100
„ one leg	9	15*
„ both legs	12	4
„ one arm and both legs	22	7
„ 4 limbs	8	—
„ uncertain	20	—
Total	370 (53%)	169 (24%)

* Increased figure is due to some early cases of paraplegia or triplegia recovering to crural monoplegia.

the permanent signs of more than trifling severity, and it is clear that a large number of the cases with early signs recover well. However, the incidence of permanent major physical disability is over 30%, and as will be seen later (Table XI) about a third of the men with penetrating wounds are drawing a 100% pension five years after wounding. It should be explained that the same case may appear in both Tables V and VI. On the other hand, though slight degrees of paresis are excluded from the permanent disabilities in Table V, the slightest

TABLE VI

INCIDENCE OF EARLY AND PERMANENT VISUAL AND APHASIC DISORDERS IN 693 CASES OF PENETRATING BRAIN WOUNDS

693 Penetrators with Focal Symptoms		
Symptom	Early	Permanent
Visual	302 (44%)	209 (30%)
Aphasic	217 (31%)	135 (20%)* (including " slight " cases)

* Entry on left in all but 7.

permanent disturbances of the visual fields or of the speech mechanism are included in Table VI. The overwhelming importance of the dominant (generally left) hemisphere in relation to aphasia is also evident.

Site of Wounding

In Fig. 2 a system of measurement is used (Russell, 1947) to record on one chart the site of wounding in a large number (631) of cases. The crosses represent wounds which were followed by post-traumatic epilepsy (306 cases), and the circles the site of wounding in 325 cases which did not develop epilepsy within five years of wounding. It will be seen that there are many examples of wounds to all parts of the brain except the brain-stem, while the limited number of cerebellar and low occipital wounds reflects the dangerous nature of wounds involving the posterior fossa of the skull. This figure does not indicate accurately the regional incidence of post-traumatic epilepsy, but it does show that the incidence is higher in some regions (e.g., the parietal lobe) than in others.

A more accurate assessment of the incidence of post-traumatic epilepsy is provided by analysing the paramount cards directly. Table VII gives the

TABLE VII

INCIDENCE OF EPILEPTIC FITS ON FOLLOW-UP AT OVER 5 YEARS IN 820 " PENETRATORS "

Epileptic fits on follow-up	356 cases (43% of total)
No fits in cases followed for—	
over 5 years	403 cases
2–5 years	21 „
1–2 years	21 „
under 1 year	19 „
Total	464 „

result of such an analysis and indicates a high incidence (43%) for the occurrence of one or more fits within the first five years after wounding. The

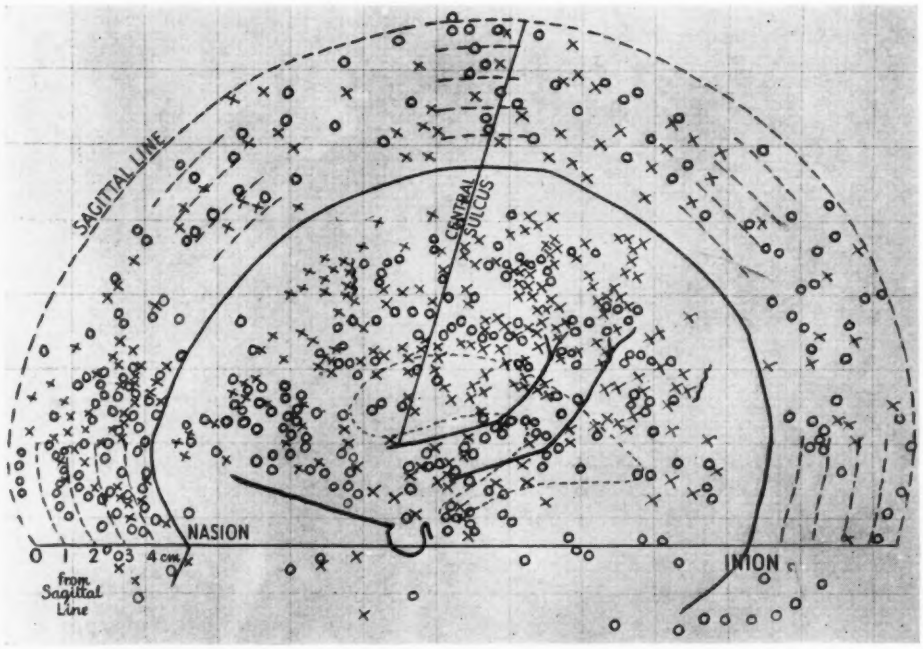

FIG. 2.—Chart to show the site of wounding in 631 cases. Charting depends on measurements taken from the skull radiographs (Russell, 1947). Wounds which lie within 5 cm. of the sagittal line are placed in the halo outside the skull outline. The cases marked X developed post-traumatic epilepsy while those marked O showed no epilepsy at a five-year follow-up.

interval after wounding at which the first of these fits appeared is given in Table VIII, and the type of fit in Table IX. This information cannot be considered very accurate as many of the cases had to be assessed from questionnaire or "fit form". However, my impression is that the incidence of post-traumatic epilepsy in these tables is an underestimate, as the doubtful cases go in the "no-epilepsy" group. Although the incidence of post-traumatic epilepsy is so high, the actual fits in most cases are so infrequent, and so easily controlled by anti-convulsant drugs, that post-traumatic epilepsy is seldom in our experience a very serious disability, a point of great importance in assessing the need for surgical treatment.

These figures for post-traumatic epilepsy show no striking change from the published records following the first world war, and this in spite of the vastly reduced incidence of infection in the present series. Further, Table X shows that the incidence of post-operative infection played no great part in the development of epilepsy in this series. These figures must cast doubt on the thesis put forward many years ago by Penfield (1927) in which he maintained that progressive gliosis in relation to a brain scar is the main factor which causes fits. Indeed this view has already failed to hold the field, as is evident from Earl Walker's recent approach (1949) to the subject of traumatic epilepsy, in which he leaves the scar alone and excises healthy-looking pieces of electrically unstable cortex in its neighbourhood.

TABLE VIII

TIME OF ONSET OF POST-TRAUMATIC EPILEPSY IN 356 CASES

Interval after Wounding of First Fit	
Under 1 month	47* cases
1–6 months	94 ,,
6–12 months	62 ,,
1–2 years	49 ,,
Over 2 years	28 ,,
Unknown	76 ,,
Total ..	356 ,,

* Includes 14 cases with no fits after first month (5 year follow-up).

TABLE IX

TYPE OF EPILEPSY IN 356 CASES OF POST-TRAUMATIC EPILEPSY

Type of Fit	No. of Cases
Focal only	46
General only	192
Focal and general	118
Total	356

TABLE X

APPROXIMATE INCIDENCE OF POST-OPERATIVE INFECTION OF SCALP, SKULL, MENINGES OR BRAIN

	No. of Cases with Post-operative Wound Infection
356 cases of post-traumatic epilepsy	61 cases (17%)
466 cases. No epilepsy	61 cases (13%)

Another popular view in recent years has suggested that a constitutional factor determines the occurrence of traumatic epilepsy. This, however, seems unimportant when the incidence is approaching 40%, nor does it offer any reason for the comparatively very low incidence in closed head injuries (less than 3%) with diffuse neuronal injury.

One cannot but look round for some other factor in the causation of traumatic epilepsy. In this connexion it should be noted that the ultimate incidence of post-traumatic epilepsy is likely to be little short of 50%, a figure which indicates even chances whether or not epilepsy occurs. It seems to me that this figure suggests that brain wounds may upset the balance between two antagonistic types of cerebral mechanisms and that the development of epilepsy may depend upon whether one or the other is the more damaged. There is certainly nothing very improbable in the suggestion that many cerebral thresholds are maintained by a balance between the two opposing mechanisms of stimulation and suppression, and that trauma may upset this balance one way or the other. Such a view adds uncertainty to the surgical treatment of traumatic epilepsy as we do not yet know how to redress the balance, but there are hopes that the future may bring new knowledge which will add to the surgeon's effectiveness in this field.

Finally, I should like to give some information regarding the social status of these pensioners. The Ministry of Pensions percentage disability five years after wounding is shown in Table XI, and the rough employment groups are given in Table XII.

TABLE XI

RATE OF PENSION AND FITNESS FOR EMPLOYMENT ON LAST FOLLOW-UP OF 606 CASES OF PENETRATING BRAIN WOUND

	Rate of Pension	No. Gainfully Employed
No pension ..	35	35
20–40%	136	136
50–70%	154	153
80–90%	72	71
100%	209	93
	606	488 (81%)

TABLE XII

TYPE OF EMPLOYMENT IN 488 CASES

Type of Employment	No. of Cases
Heavy manual	24
Light manual or unskilled	402
Intellectual or highly skilled	62
	488

It is clearly gratifying that such a high proportion (81%) are earning a living, but employment is generally unskilled and the mental adjustment to grave disability is often slow and painful. The marriage state of these cases is given in Table XIII.

TABLE XIII

SOCIAL STATUS OF 209 CASES DRAWING 100% PENSION

Social Status	No. of Cases
Single	84
*Married before wounding	75
Married since wounding	35
Not known	15

* Four separated and one divorced.

This is of importance, for the help of an understanding wife is quite invaluable to these men. Efforts made to settle the unemployed or unemployable are shown in Table XIV. Though many

TABLE XIV

OCCUPATIONAL STATE OF 117 " UNEMPLOYED " CASES

Occupational State	No.
In and out of work	23
Helping relations in shops, etc., or home	8
Rehabilitation centre or course	14
Poultry	3
Sheltered workshop	2
Mental hospital	4
Emigrated	1
No work or occupational therapy at home or Headington Hill Hall ..	62
	117

organizations assist in this type of work the contribution by our advice bureau has been, I think not unimportant. Further, the Red Cross and St. John organizations run an excellent rehabilitation centre at Headington Hill Hall in Oxford.

A little ingenuity will often find some profitable occupation for the severely disabled. Many of our cases at Headington Hill Hall suffer from severe hemiplegia and aphasia, and yet can be trained to make excellent furniture (of a value of £3 to £4 per week) in a special workshop ; one such patient also can weave three yards of tweed in four hours (selling for over £2), and another working on a lathe makes wooden lamp stands at the rate of one a day which sell for 17s. 0d.

I hope that our experience may be of interest and help to those concerned with similar problems.

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THE VISUAL FIELD DEFECTS IN SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD

BY

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The occurrence of optic atrophy as part of the syndrome of subacute combined degeneration of the spinal cord is distinctly uncommon (Woltmann, 1919 ; Smithburn and Zerfas, 1931 ; Young, 1932). A clinical review and resumé of the literature was given by Turner (1940), who reported three cases and was the first writer to comment specifically on the characteristics of the visual field defects. The purpose of this communication is to record further observations on the fields of vision in this syndrome, and to discuss their possible significance and clinical importance.

Review of the Literature

In only a few instances have the visual fields been described. Bickel's (1914) patient had a central scotoma in the left eye, and the case is quoted by Turner (1940) as a possible example of the condition. But the post-mortem findings comprised marked perivascular cellular infiltration in posterior and lateral columns, with proliferation of the vessels themselves, and it seems impossible to accept the case as one of subacute combined degeneration. Hine (1936) reported full peripheral fields with a central colour scotoma in each eye, most marked for green and very difficult to chart accurately, in his patient, whereas Talbot (1936) recorded full fields for 1° white, but noted a large relative central scotoma in each eye. Neither of these authors published charts, nor did they allude in the text to the distinction between the pericentral and centrocaecal types of scotoma. Box (1936) reported " left field full " in his patient, but the acuity in this eye was as good as $^{6}/12$ after correction and it is not stated that a specific search was made for a scotoma. Cohen (1936) described slight concentric contraction only in his two patients, but the gross reduction in visual acuity to $^{6}/60$, $^{6}/36$ and $^{6}/60$, $^{6}/60$ seems inconsistent with this finding unless the central fields were also involved by scotomata. Kampmeier and Jones (1938) mention the fields only in their second patient, saying that there was no apparent gross defect ; despite this the acuity was very seriously reduced, and they indicate that the subject was somewhat uncooperative. Courville and Nielsen (1938) report that their second patient had marked constriction of the visual fields, and though they note that the Bjerrum screen was used they do not say whether the presence of scotoma was excluded. Turner (1940) published charts from two of his three cases, all of which presented essentially centrocaecal defects barely covering the fixation point, or even falling short of it ; there was slight or moderate peripheral constriction. Traquair (1946) pictures charts of almost identical appearance from a case which, though clinical details are not given, is described as " retrobulbar neuritis in pernicious anaemia with subacute combined degeneration of the spinal cord ". In the text on another page, however, he says that the visual fields in pernicious anaemia are similar to those of Leber's disease—with a dense scotoma freely involving the fixation area, possibly fibre bundle defects, and frequent affection of the peripheral field—and do not present any distinguishing features. Walsh (1947) in his textbook mentions a case of pernicious anaemia showing bilateral field defects like those described by Turner (1940), but does not detail the signs and symptoms.

To sum up, the peripheral fields in these recorded cases are usually full or nearly so and only exceptionally do they show marked contraction. Really adequate data about the central fields are available only in the cases of Turner (1940) and Traquair (1946), all four showing a centrocaecal pattern, but Traquair gives no clinical details to permit certain identification of his case as one of subacute combined degeneration. A fifth case (Walsh, 1947) is probably identical, but categorical information is lacking both as to ocular and general clinical findings.

Clinical Observations

During the examination of a series of 112 treated and untreated cases of subacute combined degeneration of the spinal cord five instances of optic

atrophy were encountered. Two of the five patients were unable to cooperate satisfactorily in examination of the visual fields, one on account of dementia occurring as part of the neurological syndrome and the other on account of the onset of senile deterioration. The remaining three cases are described below.

Case Reports

Case 1.—A woman aged 59 was admitted to hospital in 1941 with a history of general weakness for six months and of weakness of the hands and difficulty in walking for two weeks. While in the ward she became aware for the first time of impairment of vision. She had incomplete pyramidal and posterior column signs, achlorhydria, and a red-cell count of 1,630,000 per c.mm. with haemoglobin 42%, colour index 1·31, and white cells 5,000 per c.mm. The reticulocyte count was 8·8%, and many nucleated red cells were present in the peripheral blood. There was a rapid response to parenteral liver therapy, which was continued indefinitely.

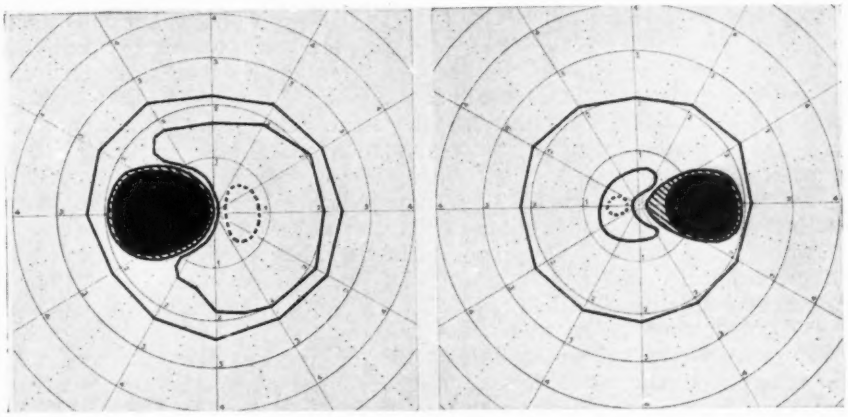

FIG. 1.—Visual fields in Case 1 (corrected for eccentric fixation). R.V. = $^{3}/_{60}$, L.V. = $^{6}/_{36}$. Objects $^{10}/_{2000}$, $^{3}/_{2000}$ white, $^{15}/_{2000}$ red; blind spot $^{40}/_{2000}$ white.

When I first saw the patient in 1948 she reported slight numbness and clumsiness of the hands, preventing the use of a sewing needle, and considerable impairment of vision, so that small print could not be distinguished and the recognition of faces at a distance was difficult. On examination the visual acuity was $^{3}/_{60}$ right, $^{6}/_{36}$ left and both optic discs showed marked pallor, maximal in the temporal halves. The visual fields (Fig. 1) showed considerable concentric contraction, greater in the right eye, and large dense scotomata of centrocaecal type with steep edges just overlapping the fixation point; on perimetry, fixation in each eye was eccentric by about 3°. The intrinsic muscles of both hands were a little weak and the power of opposition of the little fingers was lost. Tone was a little increased in both lower extremities. The tendon reflexes, with the exception of the ankle jerks, were much exaggerated, and sustained patellar clonus was present. The right plantar response was extensor and the left unobtainable, whilst the abdominal reflexes were absent. Two-point discrimination was impaired in the fingers of both hands, and vibration sense lost below the level of the iliac crests; sensation was normal in other modalities. The gait appeared normal. The other systems were normal and the blood pressure 190/100, without evidence of peripheral arteriosclerosis. A blood count showed red cells 4,930,000 per c.mm., haemoglobin 98%, and white cells 5,200 per c.mm.

The clinical features of this case, and its response to treatment, justified a diagnosis of pernicious anaemia with subacute combined system disease. Visual failure developed during the course of the illness and may fairly be considered an integral part.

Case 2.—A man aged 68 was admitted to hospital with a history of unsteadiness in walking for two years and of gradual visual failure, tingling in the finger tips, and nocturnal cramps in the feet, for one year. He smoked one ounce of mild tobacco weekly.

The visual acuity was $^{3}/_{60}$ in each eye, and both optic discs showed marked pallor. The visual fields (Fig. 2) showed considerable concentric contraction and very large pericentral scotomata extending temporally to include the blind-spots. Both legs were grossly ataxic, and the sense of passive movement was impaired in all

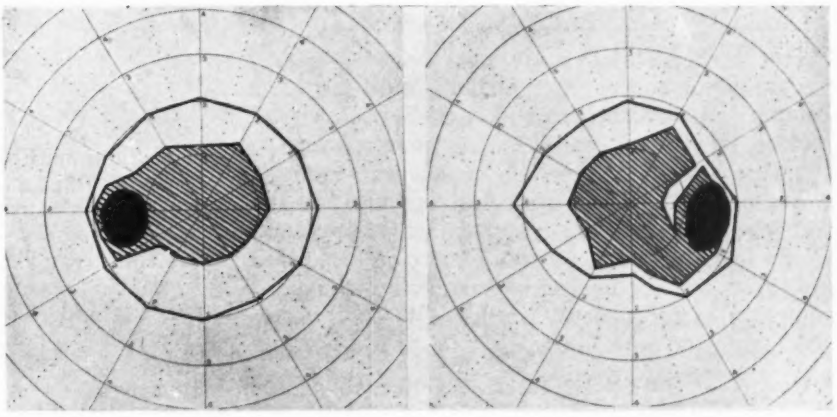

FIG. 2.—Visual fields in Case 2 before treatment. R.V. and L.V. = $^{3}/_{60}$. Object $^{5}/_{2000}$ white; blind spot $^{15}/_{2000}$ white.

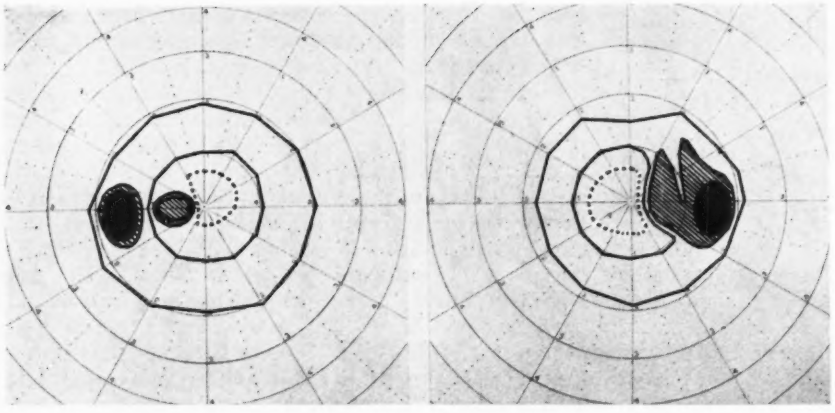

FIG. 3.—Visual fields in Case 2 after treatment. R.V. and L.V. = $^{6}/_{18}$. Objects $^{5}/_{2000}$, $^{2}/_{2000}$ white, $^{10}/_{2000}$ red ; blind spot $^{40}/_{2000}$ white.

the toes ; vibration sense was lost only in the right foot. The knee and ankle jerks were absent, but the plantar responses were flexor and the abdominal reflexes intact. The gait was grossly ataxic with a broad base, and Romberg's sign was positive. Arcus senilis was prominent, but the other systems were normal and the blood pressure only 145/100, with no significant peripheral arterial thickening. The cerebrospinal fluid was normal and the Wassermann reaction negative. A blood count showed red cells 2,840,000 per c.mm., haemoglobin 58%, colour index 0·98, and white cells 2,050 per c.mm. The sternal marrow was normoblastic, but it was discovered that liver extract had been given just before the patient's admission to hospital. A histamine-fast achlorhydria was demonstrated.

Intensive liver therapy was given, and two and a half months later the patient's paraesthesiae had almost disappeared, he was walking much better, and vision had greatly improved. The acuity was now $^{6}/_{18}$ in each eye and the fields (Fig. 3), though still showing marked concentric contraction, displayed great diminution in the size of the scotomata, which were now essentially centrocaecal in pattern, just falling short of the fixation points. The red cell count had risen to 4,520,000 per c.mm., with haemoglobin 90% and white cells 5,000 per c.mm.

Pyramidal signs were lacking and posterior column signs incomplete, but the neurological picture was consistent with the earlier phases of subacute combined degeneration, and this diagnosis was supported by haematological findings and the response to specific therapy. Visual failure presented as an integral part of the illness and likewise improved remarkably with treatment ; the consumption of tobacco was insufficient to have any bearing on the amblyopia.

Case 3.—A man aged 47 attended the out-patient clinic complaining of tingling sensations of one year's duration, involving first the fingers and toes and later spreading up the legs and trunk to the waist level ; progressive visual failure for nine months ; unsteadiness of gait for eight months ; and an abdominal girdle sensation for one month. Ten years before he had had thyrotoxicosis but recovered following operative treatment. He had been in the habit of smoking four ounces of twist weekly, but had ceased to do so six months before examination.

He had obvious exophthalmos and a red glazed tongue. The visual acuity was $^{6}/_{60}$ right, $^{6}/_{36}$ left ; the right optic disc showed temporal pallor and the left general pallor. The legs were ataxic, with impairment of the sense of passive movement and of vibration sense, but superficial sensibility appeared intact and no muscle tenderness was present. The reflexes were normal apart from exaggeration of the knee and ankle jerks. The other systems were normal and the blood pressure was 130/80. The red cells numbered 4,620,000 per c.mm., with haemoglobin 92%, and white cells 7,600 per c.mm.

One month later the patient began to deteriorate rapidly, developing retention of urine and complete inability to walk. He was admitted to hospital, where he was found to have low-grade fever, considerable oedema of both legs, profound weakness and ataxia of the legs, exaggerated tendon reflexes and extensor plantar responses with absent abdominal reflexes, absent vibration sense throughout the lower extremities, and loss of the sense of passive movement in toes, ankles, and knees. The cerebrospinal fluid was normal and the Wassermann reaction negative. A blood count showed red cells 3,460,000 per c.mm., haemoglobin 68%, colour index 0·98, and white cells 4,900 per c.mm. with normal differential count. The absolute red cell indices were all within normal limits. There was a reticulocytosis which persisted throughout the illness at a level of 3% to 4%, but the serum bilirubin and saline fragility were within normal limits and occult blood was always absent from the stools. Fractional gastric analysis showed histamine-fast achlorhydria, but the sternal marrow was normoblastic. Liver function tests showed no abnormality.

Within a few days he developed pressure sores over the sacrum and buttocks and a urinary infection. Treatment with " hepastab ", 4 ml. daily, was begun, and within a week the paraesthesiae had become much less marked. Progress was otherwise very slow, but after three and a half months all bedsores had healed and he was able to stand though not to walk ; the red cell count was 4,530,000 per c.mm., and the haemoglobin 86%. After a further three months he could walk 200 yards with the aid of a stick. The visual acuity had improved to $^{6}/_{36}$ right, $^{6}/_{18}$ partly left ; the visual fields (Fig. 4) showed bilateral centrocaecal scotomata with a slight col between fixation point and blind spot, whilst their peripheral extent was nearly full.

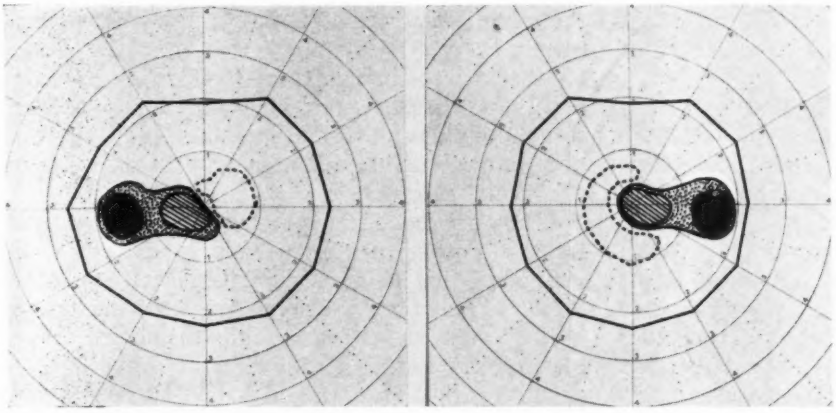

FIG. 4.—Visual fields in Case 3. R.V. = 6/36, L.V. = 6/18 pt. Objects 2/2000 white, 10/2000 red; nucleus 10/2000 white; blind spot 40/2000 white.

The gait continued steadily to improve and the red cell count reached 5,280,000 per c.mm. with a haemoglobin of 102%, but the visual acuity and visual fields displayed no further change.

This man had a normocytic anaemia with a persistent reticulocytosis of 3 to 4%, and the case did not show the haematological features of pernicious anaemia. Neurologically, however, the illness presented with obtrusive, slowly spreading paraesthesiae in all four limbs, followed by ataxic paraplegia with posterior column signs antedating pyramidal signs. This picture, associated with glossitis and histamine-fast achlorhydria, would seem to justify a diagnosis of subacute combined degeneration of the cord, and this is further supported by the response to liver therapy: slow but uninterrupted recovery followed the beginning of this treatment, whereas before its institution the symptoms were steadily aggravated without remission. The phase of rapid deterioration just before admission to hospital, with crural paralysis, sphincter disturbances, fever and oedema of the lower half of the body, is reminiscent of the classical description by Russell, Batten, and Collier (1900). The possibility that tobacco was the cause of the amblyopia had to be considered, as the patient had been a heavy smoker of twist, but cessation of the habit for six months had brought about no improvement in vision, and the onset of the paraesthesiae of the extremities three months before the beginning of visual failure strongly suggests that the latter symptom was in fact part of the major neurological disorder. Moreover vision improved *pari passu* with the other neurological functions when liver therapy was given.

Discussion

The Type of Field Defect.—The peripheral fields in these patients showed great variation, ranging from almost full extent in Case 3 to severe contraction in Case 2.

Only in Case 2 was an opportunity afforded to examine the central fields before treatment, and here the pattern was one of pericentral scotoma of about 10° radius linked to the enlarged blind spot by a rather narrower zone. Fixation and cooperation tended to be imperfect at this stage of the illness, and exhaustive examination using many different visual angles was precluded by fatigue. The central fields after treatment presented features of similarity in each of the three cases (Figs. 1, 3, and 4). The scotomata were bilateral and centrocaecal in position, with the nasal edge quite close to the fixation point. The vertical extent was variable, but the long axis was always horizontal, and in two instances (Cases 2 and 3) there was narrowing and diminished density to the nasal side of the blind spot. The scotomata were dense, with steep edges, and disproportion for colour was not present—findings consistent with the stationary condition of the lesion at the time of examination.

The close resemblance of the centrocaecal defects in these three cases to those found in the more fully reported cases in the literature is evident. The material is still limited to eight cases in all, and further observations are necessary, but it is of interest to examine the question of whether there is any special significance in this frequently occurring centrocaecal pattern.

Significance of the Centrocaecal Scotoma.—According to Lillie (1934) this scotoma has no real individuality, being merely a stage in the progress of the symptoms of an optic nerve lesion, of any aetiology, from an initial pericentral scotoma to ultimate blindness. But though this sequence may occur in some instances, there are many obvious exceptions; thus in tobacco amblyopia a symmetrical pericentral scotoma does not occur and the major defect throughout the illness lies between blind spot and fixation point. It is true that the centrocaecal scotoma has been reported in many conditions which have little in common with one another, including acute retrobulbar neuritis, Leber's disease, diabetes, syphilis, arteriosclerosis, and pressure lesions (Duke-Elder, 1940; Traquair, 1946). But, as noted by Traquair (1923), it is relatively infrequent in disseminated sclerosis and in Leber's disease, whereas it is the rule in tobacco

amblyopia, and it seems hardly possible to doubt that it is an entity with some specific mechanism of origin.

No pathological studies appear to have been made in cases of amblyopia associated with subacute combined degeneration, and ideas as to the mechanism of production of the changes in the visual fields can therefore be only theoretical and speculative. But in tobacco amblyopia many observations have been made on the morbid anatomy (Parsons, 1908 ; Duke-Elder, 1940) and there is general agreement that there is degeneration both of the papillo-macular bundle and also of retinal ganglion cells, but which of these sites represents the primary lesion remains unsettled. It is not easy fully to correlate this pathological incrimination of the papillo-macular fibres with the anatomical features of the scotoma. The papillo-macular bundle innervates the foveal area of the retina, and damage to the bundle might be expected to produce a symmetrical pericentral scotoma of about 5° radius, which in fact occurs with many optic nerve lesions. Two deductions then seem reasonable concerning the centrocaecal type of scotoma. First, involvement of macular fibres must be very unequal and asymmetrical. Second, that part of the scotoma between the 5° and 13° circles must be due to damage to extramacular fibres. As the retinal area in question is nasal to the macula these fibres must be crossed fibres situated in the nasal half of the optic nerve. The exact site of such juxtapapillary fibres in the optic nerve is still disputed, but whether it be axial or peripheral it is very difficult to conceive of a unitary lesion within the nerve which could account on any known anatomical basis for simultaneous damage to papillo-macular fibres and to this curiously selected group of nasal extramacular fibres. Anatomical considerations in fact seem strongly to favour a primary disturbance in the retina, where the affected neural elements are disposed in contiguity.

A primary retinal lesion was proposed by Parsons (1908), who suggested, as possible mechanisms, poisoning of synapses between retinal elements and retinal vascular spasm ; but the selective vulnerability of particular neurons remained unexplained. Behr (1935) on the contrary, insisted that the lesion was primary in the nerve, quoting pathological observations that the severity and extent of damage to the papillo-macular bundle was inversely correlated with the richness of its blood supply and was histologically maximal in the intracranial portion of the nerve, but correlation with the clinical features of the scotoma—referred to as " central "—was not attempted. Traquair (1923) thought that a specific anatomical site for the lesion could not be assigned, and believed that certain nerve elements might have a special affinity for the toxic substances : later (Traquair, 1946) he added that the pronounced tendency of the scotoma to lie along the horizontal meridian was suggestive of a nutritional and ultimately anatomical basis for the special susceptibility.

A new approach to the problem of a retinal basis for this scotoma has been made by Evans (1940). He claims that in some circumstances the centrocaecal scotoma may undergo transient fluctuation in size *pari passu* with variation in the angioscotoma of the main retinal vessels, and he argues that a vascular origin for this field defect is thereby demonstrated. The retinal area concerned is largely supplied by the cilio-retinal system, whether or not frank cilio-retinal arteries are visible with the ophthalmoscope : these vessels must then supply the macular fibres as they traverse the retina, though not the fovea itself which is avascular and nourished from the choroidal blood bed. A primary foveal lesion is therefore unlikely from vascular causes, but if a toxic or degenerative lesion of the macular fibres occurs, Evans (1940) suggests that " there may be a call for greater metabolic activity of . . . paramacular vessels as a gesture towards the restoration of local function ", and that such " derangements of this minute vascular tree doubtless cause interruptions in the passage of the nerve impulse from the cells in the region it supplies ", thus producing the centrocaecal field defect.

This hypothesis at once permits interpretation of the conditions found in Case 2 reported in this paper. The severe concentric contraction and the large pericentral scotoma alike suggest neuronal damage of exceptional degree. This may be supposed to call forth a response by the paramacular vessels which, though maximal, is unable to restore normal macular function. After treatment it may be presumed that the vascular response is adequate to restore function in the now less severely damaged central fibres, and thus the pericentral scotoma disappears, but the centrocaecal scotoma resulting from the vascular derangement persists, though reduced in extent. But although this theory of Evans (1940) is thus helpful, and in many other ways attractive, it is still open to criticism. It does not account for the temporal field defects sometimes observed for small visual angles between the 20° and 30° circles (Traquair, 1946). It does not explain the nature of the metabolic mechanism supposed to call forth the vascular response, nor the restriction of the phenomena to certain groups of cases with papillo-macular damage. There is also a possible *non sequitur* in that the vascular changes are presumed simultaneously responsible for restoration

of function in the macular fibres and for impairment of function in the ganglion cells and synapses in the same retinal area. However, till more detail is forthcoming than is available in the originator's brief formulation quoted above, a just assessment will not be possible.

If this hypothesis, of a dual origin, neural and vascular, for the centrocaecal scotoma, be tentatively accepted, has the occurrence of the latter in cases of subacute combined degeneration any special significance? The idea has indeed long been current that a vascular factor might explain the characteristic distribution of the lesions of subacute combined degeneration within the nervous system (Russell, Batten, and Collier, 1900; Wilson, 1940; Biggart, 1949) but a satisfactory precise formulation has never been achieved. Stannus (1944) claimed that in ariboflavinosis the lesions were situated in those parts of the nervous system with the richest capillary blood supply, and advanced the concept of a "capillary dysergia" manifesting itself by dilatation of vessels and retardation of flow, causing interference with normal cellular metabolism and derangement of tissue function. The tentative description given by Evans (1940) of dilatation of the paramacular vessels is reminiscent of this hypothesis, but the two theories differ fundamentally: with Stannus (1944) the vessels dilate because of intrinsic capillary damage of nutritional origin, whereas with Evans (1940) they dilate in response to some change in the tissues they supply. Moreover, the concepts of Stannus (1944), whatever their relevance to ariboflavinosis, cannot well explain the distribution of lesions in subacute combined degeneration, in which areas of low vascularity like the posterior columns (Stannus, 1944) are commonly involved. Neither is the problem clarified by direct comparison of the visual field changes in subacute combined degeneration with those in other forms of nutritional neuropathy. The centrocaecal form is uniform in tobacco amblyopia, which many workers consider of nutritional origin (Carroll, 1936), whilst conflicting findings are reported in the amblyopias sometimes associated with diabetes and chronic alcoholism (Duke-Elder, 1940; Traquair, 1946). In the nutritional neuropathies occurring in prisoners of war Spillane's (1947) cases presented the pericentral type of scotoma, though some were so large as to engulf the blind spot, while Graveson (1947) reported nearly 15% incidence of centrocaecal defects, 65% being pericentral and the remainder paracentral or annular.

The problem therefore is very far from solution. It can only be said that a retinal vascular factor as well as a neural factor seems probable in the genesis of the centrocaecal scotoma. In the amblyopia of subacute combined degeneration it is tempting to try to relate such a vascular factor to vascular theories of the genesis of the disease, but evidence on the question is conflicting and uninformative.

The Field Changes and Differential Diagnosis.—The observations recorded in this paper have considerable clinical importance in relation to the problem of diagnosis and treatment of the middle-aged patient presenting with subacute onset of bilateral amblyopia with centrocaecal scotoma. In my experience the commonest conditions with this clinical picture are tobacco amblyopia and a so-called chronic retrobulbar neuritis; but the possibility of subacute combined degeneration must be considered in every such case, and this is of great importance because of the chance of amelioration or cure by specific therapy, which is more effective neurologically the earlier it is applied.

The majority of cases of subacute combined degeneration can be recognized by the presence of other abnormal neurological signs. Nevertheless optic atrophy from this cause may occur before the development of signs elsewhere in the nervous system (Turner, 1940), or even before blood changes become manifest (Cohen, 1936), and in such cases diagnosis may be very difficult. Achlorhydria is a *sine qua non*, but occurs in a considerable proportion of elderly subjects without pernicious anaemia (Oliver and Wilkinson, 1933), and such points as soreness of the tongue and a family history of pernicious anaemia may assume considerable importance. If all these fail a controlled therapeutic test with liver extract may be justifiable.

Writers on tobacco amblyopia have tended perhaps to oversimplify the diagnosis. Thus Traquair (1930, 1946) emphasizes the importance of other diseases in precipitating the onset of amblyopia, and Carroll (1935) refers to a case associated with pernicious anaemia. Whether or not such patients make full visual recovery, it seems to me difficult to be sure that the essential factor was not pernicious anaemia rather than tobacco; this problem arose in Case 3 of the present series. Secondly Traquair (1930, 1946) claims that the special characters of the visual fields in tobacco amblyopia are virtually pathognomonic. But these characters, which include diffuseness of the scotoma with sloping edges and marked disproportion for colours, are merely expressive of a diffuse lesion producing partial impairment of function of many nerve elements, but destroying only a few. Now many cases of subacute combined degeneration show very slow progression of spinal signs and symptoms, and if the ocular lesions advance at a similar rate

it is clearly not impossible that a case in the early stages of amblyopia might present signs of partial impairment of retinal function similar to those of tobacco amblyopia. The description of Hine (1936), quoted earlier in this paper, is illustrative of this point, even though he does not detail the exact location of the scotoma.

" Chronic retrobulbar neuritis " is not a very well defined entity. One group of cases is alluded to by Duke-Elder (1940), who emphasizes the resemblances to the toxic amblyopias rather than to the inflammatory lesions, the frequent bilateral involvement, the slow onset, chronicity, and poor prognosis. Traquair (1930) also describes similar cases presenting centrocaecal scotomata, and during the period in which the cases of subacute combined degeneration here reported were collected I have seen four cases approximating to this clinical picture. There was no indication of the aetiology. All were over 50 and the age incidence is not dissimilar to that of pernicious anaemia. Where free acid is present in the gastric juice, diagnosis is less difficult, but if there is achlorhydria, a controlled therapeutic trial with liver extract may be desirable.

Summary

The literature of optic atrophy associated with subacute combined degeneration of the spinal cord is reviewed with reference to the changes reported in the fields of vision.

In a group of 112 cases of subacute combined degeneration five instances of optic atrophy were encountered ; in three of these accurate assessment of the visual fields was possible, the essential defects being scotomata of centrocaecal type with varying degrees of peripheral contraction.

The significance of these observations is discussed and the diagnostic importance noted.

I wish to thank Dr. F. R. Ferguson and Dr. J. F. Wilkinson for permission to quote cases under their care in the Departments of Neurology and Haematology at the Manchester Royal Infirmary.

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AN INVESTIGATION INTO THE EFFECTS OF GLUTAMIC ACID ON HUMAN INTELLIGENCE

BY

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Since 1943 there have been many reports of investigations conducted to determine whether the oral administration of supranormal quantities of glutamic acid is followed by an improvement in cognitive and other functions. Both rats and human beings have been used as subjects, and the literature shows that both positive and negative results have been obtained. Working with rats, Albert and Warden (1944) and Zimmerman and Ross (1944) have reported improvements in performance in problems of the maze type, but point out that no significant changes in weight or growth were observed. Hamilton and Maher (1947) reported that the experimental animals " showed a significantly higher activity level than the controls " on the three-table test of " reasoning ", but that they observed no significant differences in actual test scores on this test or on tests of timidity which were administered after the three-table test. Entirely negative results were obtained by Stellar and McElroy (1948) and Marx (1948) from measures of test performance and of weight, and the latter also observed no increases in the activity level. With human beings as subjects, Price, Waelsch, and Putnam (1943) and Waelsch and Price (1944) have reported that patients suffering from petit mal improved in behaviour and in the frequency and severity of their seizures. With mentally retarded subjects, improvement in performance on cognitive tests has been reported by Gasorek (1948), Zimmerman, Burgemeister, and Putnam (1948), and Albert, Hoch, and Waelsch (1946). The last named reported improvement on personality tests also. Zimmerman, Burgemeister, and Putnam (1949a, and b) reported improvements in mongoloid patients on verbal tests, and in behaviour and general physical condition. The same investigators (1946, 1947) found in mentally retarded patients suffering from convulsive disorders that they improved in performance on psychological tests of personality and of cognitive functions, as well as in activity level and behaviour. Schizophrenic subjects were used by Ewalt and Bruce (1948) and Kitzinger, DeVere, Cartwright, and Shapiro (1949), who reported improvements in personality (as estimated by tests), activity level, and behaviour. Harney (1950) found that glutamic acid had a beneficial effect upon the mental age, personality, and school achievement of retarded girls.

The present experiment was designed to test the hypothesis that the oral administration of glutamic acid to human subjects would be followed by improvements in their scores on psychological tests of intelligence, both of the verbal and the performance type. In view of the reports of improvement in personality and behaviour, the body sway test was also included, on account of its brevity, simplicity, and its correlation with neuroticism (Eysenck, 1947). To this was subsequently added the static ataxia test, which has the same advantages (Eysenck, 1947). The additional hypothesis was that the administration of glutamic acid would be followed by a decrease in the scores on these tests of neuroticism.

The administration of the experiment, including the selection and matching of the subjects, was the responsibility of the psychiatrist (J. R. Milliken). The actual testing, and the analysis of the results after the completion of the testing, were carried out by the psychologist (J. L. Standen), who was unaware which subjects were experimental and which control until the testing was finished.

Plan of the Experiment

Three main groups of subjects were chosen : (1) adult patients in a mental defectives' institution ; (2) child patients in the same institution ; (3) boys of a normal range of intelligence, living in a home.

The last-named group was subdivided into " seniors " and " juniors ", the seniors being all those over the age of 10, and those under 10 who were able to complete the Thurstone primary mental abilities test which was taken by all the boys over 10. The remainder of the boys constituted the junior group.

It was found possible at a later stage of the experiment

to add another group of adult defectives, so that the experiment was actually conducted with five distinct groups of subjects. For convenience of reference, they were described as " Adult Defectives Group I ", " Adult Defectives Group II ", " Defective Children ", " Senior Normals ", and " Junior Normals ".

Each of these groups was divided, after the initial testing, into an experimental section (" E ") and a control section (" C "). In every case, the members of the E section received glutamic acid, and the members of the C section received a control mixture during the same period. At the end of the period (four months in the case of the three defective groups, and three in the case of the normals) every subject was again tested, with the same or equivalent tests as on the first occasion. The roles of the two sections within each group were then reversed, so that subjects who were formerly experimental became controls, and vice versa, for a second period of treatment of the same duration as the first, at the end of which the test battery was administered for the third time.

At the beginning of the experiment each subject in the E section was matched as closely as possible, on the basis of age, sex, and intelligence, with a subject in the corresponding C section.

Selection of the Subjects

Adult Mental Defectives, Group I.—A preliminary selection was made of 88 adult patients in the Manor Hospital, Epsom, who would be in the 21–29 age group when the experiment began. From this number there were then rejected (*a*) those with a history of epilepsy or organic nervous disease; (*b*) those who showed any signs of organic nervous disease on physical examination; (*c*) those who were in isolated wards of the hospital in numbers insufficient to justify the special supervision necessary; (*d*) those whose I.Q.s were below 45 on the new Stanford-Binet scale.

There were 36 remaining, of whom only 26 continued to receive glutamic acid or the placebo regularly for four months, and 23 then completed the second period of four months. The I.Q. range of the 26 was 48–72. Those who failed to complete the experiment did so for reasons beyond the experimenters' control.

Defective Children.—All children in the hospital whose ages were between 10 and 14 years were first selected, and from these were rejected those who fell into categories (*a*), (*b*), and (*d*) as defined above. There remained 20, of whom 16 completed both the four month periods. Their I.Q. range was 41–66.

Normal Boys.—All the boys in Dr. Barnardo's Home, New Lodge, Windsor, whose ages were between six and 15 were first chosen, and from these were rejected those who fell into categories (*a*) and (*b*), and also those who were likely to leave the home before the end of the experiment. Of the number remaining, all those over 10 were tested with the Thurstone primary mental abilities group test. Those between eight and 10 were given the same test, and the ten boys who were most successful, as measured by the sum of the scores on the word-meaning and the reasoning tests, were included in the senior group. The remainder constituted the junior group. Sixty-one members of the senior group completed the first period of three months, and 56 completed the second period. In the junior group, 24 completed the first period, and 21 the second period. The members of the senior group were tested with the Wechsler-Bellevue intelligence scale I, and their I.Q.s ranged from 65 to 112, with the exception of two boys, whose I.Q.s were 58. The I.Q. range of the juniors, who were tested with the new Stanford-Binet scale, was 67–112.

Adult Mental Defectives, Group II.—This group was added when the second stage of treatment had been reached by Group I. It consisted entirely of women, who were selected according to the same criteria as Group I, except that the lower I.Q. limit was set at 40. Twelve patients became available, with I.Q.s ranging from 43 to 74. They received only one period of treatment (four months).

The subjects in each group were paired on the basis of age, sex, and intelligence (i.e. the Binet I.Q. in all cases except the senior boys, whose intelligence was measured, for this purpose, by the sum of the scores made on the word-meaning and the reasoning sections of the P.M.A.), and the result of a coin-toss determined which member of each pair was allocated to the E section of the group.

Materials and Administration

The l-glutamic acid solution (sodium glutamate) was made up by mixing l-glutamic acid in distilled water and neutralizing with caustic soda solution to *p*H 7, the strength of the final solution being such that 1 g. glutamic acid was contained in 4 ml. Sacch. ust. was added to approximate the colour to that of the control solution. The control solution was made up of yeast extract 2, sodium chloride 3, aq. chlor. 25, water to 100.

Both these solutions had a similar appearance and taste. They were either made up freshly each week or stored in a refrigerator up to a maximum of three weeks. As a check on the l-glutamic acid content of the solution used, two specimens were determined by l-glutamic acid decarboxylase. Both were initially described as containing 25 g. glutamic acid per 100 ml. The first, tested after five months, during nearly the whole of which time it had been kept in a refrigerator, contained 20·1 g./100 ml. The second, tested after three weeks kept mostly at room temperature, contained 19·9 g./100 ml.

The solutions were administered by mouth in water twice or three times a day, with or before a meal. In all cases the beginning dose of glutamic acid was 12 g. per

day, and this was increased to a maximum of 20–36 g. per day in different subjects. Those in the control groups received corresponding amounts of the control solution.

In all cases the period of administration of each solution was not less than 12 weeks in the two normal groups, and 15–16 weeks in the three defective groups. After stopping the administration of either solution to any subject, the intelligence and other tests were administered after an interval of not less than six hours nor more than two days ; within a week of the discontinuance, the administration of the other solution was begun.

The l-glutamic acid and control solutions were labelled " Mixture Z " and " Mixture A ", and neither the staff nor the subjects were aware which mixture contained glutamic acid.

Clinical Progress

Before the treatment began the subjects were interviewed, examined physically, and told that they were to be given a special kind of tonic, which, it was hoped, would make them quicker, and that they would be tested before and after to find out if they had benefited. With a few exceptions they seemed anxious to cooperate, and in only five cases was it necessary to discontinue the treatment because of the subject's refusal to take the tonic.

The noticeable effects of the administration were few. In two adults vomiting occurred on several occasions after glutamic acid, but not after the control mixture. Many complaints of a feeling of nausea, particularly in the morning, were reported. Among the children, 28 complained of feeling sick after the glutamic acid, and four after both solutions. Six children vomited on several occasions after glutamic acid.

No other effect was noted throughout the whole period of the experiment, except that the Superintendent of the boys' home noted that two of the boys, generally difficult to manage and subject to violent outbursts of temper, had ceased to have any outbursts of temper while they were receiving Mixture Z (glutamic acid), but that within one week of starting to have Mixture A, their former behaviour had reasserted itself. One of the boys was then put on Mixture A and the other on Mixture Z. During the following week the boy on the control mixture had several temper outbursts, while the other had none. At the beginning of the next week the mixtures were exchanged, and during this week neither of the boys was reported to be difficult. Eight months after the cessation of the treatment, the Superintendent reported that both boys had reverted to their former behaviour ; arrangements are being made for them to resume the treatment. The I.Q. (Wechsler) of one of the boys, aged 14 years 3 months at the beginning of the experiment, was 58. It had increased to 68 after three months on the control mixture, and to 73 after three months on glutamic acid. The corresponding I.Q.s of the other boy, aged 10 years 5 months were 78, 83, and 86. Increases of this order were frequent in both the E and C sections of the group (senior normal).

In view of the few side-effects noted, it was decided to give rapidly increasing doses of glutamic acid to a small group of subjects in whom no effects had previously been noticed. Four women in the 21–29 age group and four defective boys in the 10–14 age group were selected, and were given a sludge of glutamic acid powder in water, starting with 24 g. per day in divided doses and increasing by 12 g. per day. On the first and second days, due to a misunderstanding, the four boys each received 72 and 108 g., without showing any consequences save a slight feeling of nausea. After reverting to the planned dosage, they and the four adult subjects continued to have increasing doses until each was having 96 g. of glutamic acid per day. After one week no effects had been noticed in the adults, but two of the children were more active and excitable.

The Tests

For the defective adults Group I, the defective children, and the normal boys junior group, the following battery, known as " T_1 ", was used at the beginning of the experiment, before any medication had been started.

Revised Stanford-Binet, Form L
Kohs' blocks (Drever-Collins version)
Manikin and profile object assembly test (Drever-Collins)
Healy picture completion test No. 1 (Drever-Collins)
Goodenough " drawing a man " test
Body sway test of suggestibility

The batteries used for the second and third testing sessions (" T_2 " and " T_3 " respectively) were the same as the above, except that the static ataxia test was introduced immediately before the body sway test, and that the Binet form M was used in place of form L in T_2. In T_3, form L was used again.

The defective adults Group II, who were, as previously indicated, added when the other defective groups were entering the second phase of the experiment, were given the same battery that has already been described. In their T_1, the Binet form M was used, and form L in their T_2. The static ataxia test was included on both occasions.

The battery used for the normal boys senior group was as follows :

Wechsler-Bellevue intelligence scale I
Goodenough " drawing a man " test
Static ataxia test (in T_2 and T_3)

Body sway test
Thurstone primary mental abilities group test
Rorschach group test (using lantern-slides of the ink-blots)
Maudsley letter series group test

After the rejection of those subjects who failed to satisfy the criteria previously stated, a few more were lost from each group, either because they could not be matched sufficiently closely, or because of refusal to take the mixture, or because of unexpectedly becoming unavailable within a few days of the completion of T_1. All who were rejected for any of these reasons were classified as " not used ", and their mean I.Q.s have been compared with the mean I.Q.s of those who were used. Table I shows the results of these comparisons.

In the case of the defective children, where a highly significant difference occurs, the reason for the rejection of all three subjects was inability to match.

At later stages in the experiment a few more subjects were lost for reasons beyond the control of the experimenters, and it also happened occasionally that a subject was not able to take all the tests in the battery. Due to the disturbance of the matching thus entailed, a modification was introduced into the statistical treatment of the data.

The Statistical Technique

The hypothesis to be tested was that the mean improvement of the experimental section on any test would be significantly greater than the corresponding improvement of the control section.

If G represents the effect attributable to glutamic acid, and P the effect attributable to the placebo, it is possible to derive from the test scores obtained in this type of experiment an estimate of the difference G–P, representing the excess of the improvement due to glutamic acid over that due to the placebo, and to test the significance of this estimate. Since the sign of this difference is specified by the hypothesis (positive in all cases except that of the static ataxia and body sway tests, where the sign is negative), the significance of the estimated difference can be tested by the one-tail t-test when the difference is in the predicted direction. Those differences which are not found to be in the predicted direction show immediately without testing that the hypothesis is not confirmed.

The procedure adopted was as follows. From the score of each subject on a test in T_2 was deducted his score on that test in T_1. The resulting difference, D, with its sign, represented the subject's improvement (or otherwise) during the first period of the experiment. If the mean improvement of the experimental subjects is written $\bar{D}_e$, and the mean improvement of the controls is written $\bar{D}_c$, then the expression $\bar{D}_e - \bar{D}_c$ represents that function of the test scores which was taken as the estimate of G–P. The effects of growth, practice and errors were assumed to be equal, on the average, between the experimental and control sections of the group tested.

The same procedure was adopted in the treatment of the scores made on the tests in T_2 and T_3, which were administered at the beginning and end respectively of the second period of the experiment. In this case, D^1 represents the score on a test in T_3 minus the score on the same test in T_2, and it can be shown algebraically that the function $\bar{D}^1_e - \bar{D}^1_c$ is an estimate of twice the difference G–P, on the same assumption that the effects of growth, practice, and errors cancel out.

The technique of analysis of variance, of which the ordinary t-test is the simplest case, was used for the treatment of the data. It was originally intended to use that version of the technique which has been devised for data obtained from matched groups, such as were arranged for this experiment, but owing to the loss of some of the subjects after the matching had been carried out, and to the already small numbers of subjects in the groups, it was decided, in consultation with A. Lubin, to disregard the matching entirely, and to apply the analysis of variance technique in its ordinary form. There was no reason to suppose that this introduced any bias. Fisher states (1941) that

> " In cases in which each observation of one series corresponds in some respects to a particular observation of the second series, it is always legitimate to take the differences and test them . . . as a single sample ; but it is not always desirable to do so. A more precise comparison is obtainable by this method only if the corresponding values of the two series are positively correlated, and only if they are correlated

TABLE I

Group	Test	Numbers		Mean I.Q.s		Variances		Significance of Difference
		Used	Not Used	Used	Not Used	Used	Not Used	
Defective adults I ..	Binet	26	9	58·4	65·0	72·2	152·0	—
Defective adults II ..	Binet	12	2	57·8	61·5	163·4	0·5	—
Defective children ..	Binet	16	3	49·2	61·7	51·8	369·3	·1%
Senior normal boys ..	Wechsler	61	16	88·1	86·3	147·7	169·2	—
Junior normal boys ..	Binet	24	4	95·0	80·0	142·1	86·0	2·5%

to a sufficient extent to counterbalance the loss of precision due to basing our estimate of variance upon fewer degrees of freedom."

In the present case, using the method for matched groups (i.e. the first method described by Fisher) would have entailed the loss of unmatched subjects as well as half the total number of matched subjects in each group, for the purpose of computing the number of degrees of freedom available. It should be noted that the two " series of observations " which were compared were not the actual scores on the tests, but the differences between the scores on successive administration of the tests.

The Results

Table II shows the results obtained from the test scores made by members of four of the groups, and the results from the fifth group are shown in Table III. The " drawing a man " test, and the group Rorschach and Maudsley letter series have not yet been scored, and their results will form the subject of a later report.

Inspection of the cognitive test results in Table II shows that in no case where $\overline{D}_e - \overline{D}_c$ (i.e. the estimate of G–P) is positive, is it significant. In fact, t was found to be less than unity in every such case. For the static ataxia and body sway tests a negative value of G–P was predicted, since improvement in personality would be expected to be associated with decreased sway under the conditions of these tests. Negative values of $\overline{D}_e - \overline{D}_c$ occur seven times in Table II, and of these seven negative values, one is significant at the 5% level and one at the 1% level, by the one-tail t-test. In four of the remaining five cases, t was less than unity.

Table III shows the results obtained from the analysis of the scores made by members of the normal senior group on the ten tests which constitute the Wechsler scale I, the five tests of which the P.M.A. group test is comprised, and the static ataxia and body sway tests. Of the three values for $\overline{D}_e - \overline{D}_c$ provided by the latter, only one is negative as predicted, and it is not significant. Twenty estimates of G–P are provided by the Wechsler results, and of these 20, one is significant at the 5% level, three at the $2\frac{1}{2}$% level, and one at the 1% level. In only one other case was t greater than unity. By chance alone, one result out of 20 would be expected to be significant at the 5% level.

TABLE II

Group	Statistic	Binet Mental Age (Months)		Kohs' Blocks (Raw Scores)		Object Assembly (Raw Scores)		Picture Completion (Raw Scores)		Static Ataxia (Half-inches)		Body Sway (Half-inches)	
		E	C	E	C	E	C	E	C	E	C	E	C
Defective Adults Group I	First Period :												
	Number ..	14	12	14	12	14	12	14	12			12	12
	Mean Gain ($\bar{D}$)	9·21	14·83	2·71	3·00	1·00	1·92	1·36	1·75	—		−0·33	−0·08
	Variance ..	75·26	63·61	1·91	26·36	19·38	26·99	14·71	8·02			2·24	16·45
	Significance ..	—		—		—		—		—		—	
	Second Period :												
	Number ..	10	13	10	13	10	13	10	13	10	13	8	13
	Mean Gain ($\bar{D}^1$)	−4·20	0·69	0·60	0·85	0·00	1·31	1·40	1·38	0·40	−0·23	−1·12	0·85
	Variance ..	52·18	39·90	6·93	9·81	14·00	8·90	4·93	10·09	3·38	1·69	2·70	1·97
	Significance ..	—		—		—		—		—		<1%	
Defective Adults Group II	Only Period :												
	Number ..	6	6	5	6	6	6	6	6	6	4	6	4
	Mean Gain ($\bar{D}$)	3·33	−1·17	1·60	2·33	1·83	2·00	1·67	2·50	−0·33	2·75	−0·54	0·50
	Variance ..	98·67	125·77	0·80	16·27	10·57	11·20	14·67	4·70	3·47	2·92	16·57	0·33
	Significance ..	—		—		—		—		<5%		—	
Defective Children	First Period :												
	Number ..	8	8	8	8	8	8	8	8			8	7
	Mean Gain ($\bar{D}$)	1·25	3·37	1·50	1·25	0·25	−0·25	2·25	3·00	—		1·75	2·14
	Variance ..	4·50	21·98	5·43	3·36	3·14	14·86	21·93	12·86			11·07	4·48
	Significance ..	—		—		—		—		—		—	
	Second Period :												
	Number ..	8	8	8	8	8	8	8	8	7	8	7	8
	Mean Gain ($\bar{D}^1$)	1·75	0·25	−0·50	0·25	3·37	1·50	0·87	1·62	0·14	−1·00	−0·86	−1·75
	Variance ..	4·96	11·64	2·75	3·44	18·55	15·71	26·41	4·84	1·48	2·86	5·81	14·50
	Significance ..	—		—		—		—		—		—	
Normal Boys Junior Group	First Period :												
	Number ..	12	12	12	12	12	12	12	12			12	11
	Mean Gain ($\bar{D}$)	3·83	2·50	1·75	1·67	1·58	0·67	1·67	1·42	—		−1·25	−1·00
	Variance ..	93·61	101·36	0·75	1·33	10·81	4·24	13·33	19·90			4·85	15·09
	Significance ..	—		—		—		—		—		—	
	Second Period :												
	Number ..	11	10	11	10	11	10	11	10	10	10	10	10
	Mean Gain ($\bar{D}^1$)	5·45	5·10	0·36	1·20	1·64	0·00	2·64	3·20	−0·20	−0·30	0·50	0·60
	Variance ..	102·47	21·88	4·65	6·18	17·65	17·78	8·25	7·73	7·73	8·46	0·94	3·38
	Significance ..	—		—		—		—		—		—	

TABLE III

Normal Boys : Senior Group			First Period							Second Period						
		Test	Numbers		Mean Gains		Variances		Significance	Numbers		Mean Gains		Variances		Significance
			N_e	N_c	$\bar{D}_e$	$\bar{D}_c$	V_e	V_c		N_e	N_c	$\bar{D}_e$	$\bar{D}_c$	V_e	V_c	
Wechsler (Raw Scores)	Verbal	General comprehension	30	31	1·17	0·64	4·97	3·97	—	27	29	0·22	−0·79	3·03	2·60	2·5%
		Arithmetic	30	31	0·97	−0·03	1·55	2·77	1%	27	29	0·00	−0·14	2·69	1·12	—
		Similarities	30	31	1·63	1·32	5·21	5·16	—	27	29	0·41	0·52	4·63	3·83	—
		Digit repetition.. ..	30	31	0·30	−0·13	2·15	2·05	—	27	29	0·48	0·31	1·26	1·29	—
		Vocabulary	30	31	0·35	1·00	2·09	3·25	—	27	29	0·00	0·40	2·92	1·93	—
	Performance	Picture arrangement ..	30	31	2·10	1·58	10·44	6·92	—	27	29	1·18	1·45	6·93	14·47	—
		Picture completion ..	30	31	1·50	1·29	4·67	1·95	—	27	29	0·63	0·28	1·24	2·99	—
		Object assembly.. ..	30	31	1·77	2·26	3·23	15·20	—	27	29	2·11	1·59	9·64	8·82	—
		Block design	30	31	3·37	3·26	15·76	14·60	—	27	29	3·07	0·86	18·69	8·77	2·5%
		Digit symbol	30	31	5·32	2·81	37·04	26·73	5%	27	29	2·63	0·19	12·47	17·56	2·5%
P.M.A. (Raw Scores)		Word meaning	27	30	1·18	3·40	15·00	11·08	—	26	25	2·04	0·88	22·44	31·53	—
		Space	30	31	7·60	6·26	63·90	91·73	—	27	28	2·41	2·86	27·25	65·24	—
		Reasoning	29	30	1·76	1·00	11·62	14·90	—	26	27	0·69	0·37	9·82	26·63	—
		Number	30	31	1·77	0·35	20·05	17·70	—	27	28	1·37	−1·71	21·63	31·47	2·5%
		Word fluency	30	31	1·53	0·71	22·46	31·88	—	26	27	3·04	1·33	21·96	21·69	—
Static ataxia (half-inches)			—	—	—	—	—	—	—	26	29	1·31	0·55	3·82	5·68	—
Body sway (half-inches)			28	26	0·93	0·04	9·70	9·08	—	26	29	0·00	0·14	3·36	8·91	—

Of the ten estimates of G–P derived from the P.M.A. scores, one is significant at the $2\frac{1}{2}\%$ level. By chance, one out of ten would be expected to be significant at the 10% level. Values of t greater than unity were found in two other cases in the P.M.A. results.

It will be observed that, whereas in Table II 16 of the 28 values for $\bar{D}_e$–$\bar{D}_c$ derived from the cognitive test scores are negative, Table III shows only seven out of 30 values for the same function to be negative.

Discussion

It seems fairly clear that the cognitive test results in Table II (i.e. those of the three defective groups and the junior normal group) afford no evidence whatever in favour of the hypothesis. Not only is none of the positive differences significant, but there are approximately as many negative as positive differences, which is in accord with chance expectation.

The results of the ataxia and suggestibility tests are more difficult to interpret. There are 14 such results altogether, including those in Table III, as the tests were exactly the same for the senior normal group. Eight of these, that is, just over half of them, are in the predicted direction, which, again, is in accordance with chance expectation ; but two of them are significant, one at the 1% level, and one at the 5% level. Strictly speaking, this is not what would be expected on a chance hypothesis, but the departure from a chance prediction is scarcely large enough to be regarded as affording any but the slenderest evidence in favour of the hypothesis of personality improvement.

The results obtained from the Wechsler scores of the senior normal group (Table III) show some departure from the general pattern of the other results. These scores provide 20 estimates of G–P or, more precisely, ten of G–P and ten of 2(G–P) : the distinction is immaterial in the present context. Fifteen of these estimates are in the predicted direction, and five of them are significant. On a chance hypothesis, ten would be expected to be positive, and one to be significant at the 5% level. It does appear, therefore, that in this case there is some slight evidence in favour of the main hypothesis. A difficulty arises, however, from the fact that the tests used are not independent. The tests which yielded the significant differences are the digit symbol (5% and $2\frac{1}{2}\%$), block design ($2\frac{1}{2}\%$), general comprehension ($2\frac{1}{2}\%$), and arithmetic (1%). Examination of the table of inter-test correlations given by Wechsler (1944), based on 355 cases in the 20-34 age group, discloses that the inter-test correlations under consideration range from 0·429 to 0·538 The table shows eight inter-correlations higher than 0·538 and 17 lower than 0·429. The highest in the table is 0·721, the median is 0·456, and the lowest is 0·155. If these published (American) inter-correlations are accepted as a basis for comparison in the present case, the objection that the tests are not independent appears to have force.

An alternative approach is to consider the character of the tests which have yielded significant results. In all except one (general comprehension) the score of the subject depends partly on his speed of performance. This suggests that the observed effect of glutamic acid on the test scores may be explicable in terms of a general improvement in mental and physical alertness, or of a raising of the general activity level, as reported by other investigators. If this were so, then significant differences would be expected in the P.M.A. scores, since the

five tests in this battery are all rigorously timed. Table III shows that eight of the ten estimates of G–P [or 2(G–P)] derived from these scores are in the predicted direction, and one of them is significant at the $2\frac{1}{2}\%$ level. Although this is slightly above chance expectation, it is less so than in the case of the Wechsler scores. It is unlikely, therefore, that improvement in alertness, activity, or speed because of glutamic acid accounts for the improvement in the Wechsler scores.*

The general conclusion must be that the changes in the test scores of the subjects who were fed with glutamic acid in this experiment have provided little or no evidence in favour of the hypotheses which were to be tested.

The glutamic acid was administered in this experiment as a solution, neutralized with caustic soda : the New York investigators administered it suspended in water. As there is a possibility that the effects of these two modes of administration might be different because of the large amount of alkali received in the former, a subsidiary experiment was carried out by Dr. D. L. Davies. Since it was not practicable to determine the glutamate level in the blood at regular intervals after ingestion, because of the large quantity of blood required for each estimation and the uncertainty as to the range of individual variation, it was decided to measure the total acidity of the urine, and the serum alkali reserve after glutamic acid and after sodium glutamate, in order to test the correctness of an assumption that on an ordinary mixed diet no difference in the effect upon alkali reserve would be found. Two patients were studied. Patient A, aged 27, was observed over a period of five weeks in hospital. His diet was the ordinary hospital fare. During the first week he received no drugs. During the second week he received 10 g. of sodium glutamate b.d. for the first five days ; on the sixth day the morning dose was doubled and on the seventh day both doses were doubled. During the third week no drugs were administered. During the fourth week he received 10 g. of glutamic acid powder for the first five days ; on the sixth day the morning dose was doubled and on the seventh day both doses were doubled. During the fifth week no drugs were administered. Throughout this period 24 hour specimens of urine were collected, checked by the estimation of total creatinine, and subjected to titration of total acidity by Folin's method, the results being expressed in ml. $\frac{N}{10}$ alkali. Every Monday, Wednesday, and Friday morning at 11 a.m., with the patient resting in bed for at least 30 minutes, venous blood was taken for the estimation of serum alkali reserve by Van Slyke's titration method, the result being expressed in vols. of CO_2/100 ml. Patient B, a man aged 39, suffering from a chronic anxiety state, was subject to the same procedures except that he received glutamic acid on the days when Patient A received sodium glutamate, and vice versa. This was to remove any subjective bias in the technical assistants who did not know which drug the patients were receiving. In neither patient was there evidence of impairment of kidney or liver function. No symptoms suggestive of acidosis or alkalosis were observed. The results are shown in Table IV on page 54.

Although the expected shifts in the total titratable acidity of the urine occurred, the fluctuations in the alkali reserve followed no such clear-cut trend. Indeed the lowest reading in Subject A was obtained in the initial control period after he had recently finished strenuous physical exercise. The changes in the level of the alkali reserve were evidently well within the normal physiological range. Any difference between the effects obtained after glutamic acid and those obtained after sodium glutamate cannot be attributed to different effects upon the alkalinity of the serum.

* A small experiment, designed similarly to that described in this paper, was conducted by Dr. B. H. Kirman and Miss S. M. Cox at the Fountain Hospital, Tooting. The subjects were three pairs of children, with I.Q.s ranging from 36 to 58 (Stanford-Binet), and the test battery consisted of a variety of standard verbal and performance tests. The period of administration was three months, which was repeated with the subjects in reversed roles. No significant evidence of improvement due to glutamic acid was obtained, but the biggest increases observed in the experimental subjects were those in the Porteous maze test.

Summary

Two groups of mentally defective adults, one group of mentally defective children, and two groups of normal boys, were divided each into an experimental and a control section. Before and after treatment with glutamic acid or with an indifferent substance, each subject was given verbal, performance, and personality tests. After the second test administration each subject was transferred to the opposite section for a further period of treatment, at the end of which the tests were administered for a third time. The results of the cognitive tests provided no evidence in favour of the hypothesis that glutamic acid improves cognitive functioning, except in one group of normal boys, whose findings yielded slight but equivocal evidence in favour of the hypothesis. For the additional hypothesis, that scores on the personality tests would be improved, there was no evidence.

We wish to record our indebtedness to Dr. H. E. Magee, of the Ministry of Health, for advice regarding the choice of a home for normal children, and to Dr. Gilmore and the authorities of Dr. Barnardo's Homes for permission to conduct part of the trial in New Lodge, Windsor ; to the Superintendent, Mr. Mace, and to Mrs. Mace and the staff of the New Lodge, Windsor, to

TABLE IV

	Patient A		Patient B	
	Total Titratable Acid in ml. N/10 alkali (24 hour excretion)	Serum Alkali Reserve Vol. CO_2/100 ml.	Total Titratable Acid in ml. N/10 alkali (24 hour excretion)	Serum Alkali Reserve Vol. CO_2/100 ml.
Week 1	(No drugs)		(No drugs)	
8–9 March	217	76	298	71
9–10 „	267	—	163	—
10–11 „	194	66*	240	70
13–14 „ ..	182	75	158	72
14–15 „	272	—	209	—
Week 2	(Sodium glutamate)		(Glutamic acid)	
15–16 March	144	79	269	69
16–17 „	139	—	261	—
17–18 „	141	74	365	67
20–21 „	128	80	197	76
21–22 „	194	—	310	—
Week 3	(No drugs)		(No drugs)	
22–23 March	140	71	232	71
23–24 „	168	—	170	—
24–25 „	206	70	246	64
27–28 „	266	69	230	69
28–29 „	246	—	166	—
Week 4	(Glutamic acid)		(Sodium glutamate)	
29–30 March	203	69	81	77
30–31 „	306	—	72	—
31 March–1 April ..	217	66	69	75
3–4 April	240	72	107	82
4–5 „	316	—	97	—
Week 5	(No drugs)		(No drugs)	
5–6 April	192	70	103	69
6–7 „	233	—	92	—
7–8 „	256	71	329	70
10–11 „	331	—	249	—
11–12 „	196	70	157	69
12–13 „	205	—	225	—

* This reading was obtained within 30 minutes of finishing physical exercise.

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BOOK REVIEWS

Psychology and Mental Health. By J. A. Hadfield. 1950. London: George Allen and Unwin. Pp. 444. Price 18*s*.

This book is divided into three parts. In the first there are chapters on the scope of mental health, the sources of behaviour, types of character traits and delinquency, the psychoneuroses biologically considered, and the general aetiology of the psychoneuroses. The second part discusses the various neuroses individually, and the third their treatment. The author's viewpoint is illustrated by his statement that "it is generally agreed by psychopathologists" that the psychoneuroses and many behaviour disorders are traceable in their origin to abnormal conditions in the early years of life, from which he properly concludes that if this is so, it should be possible by providing the right conditions in childhood to prevent the occurrence of these disorders. Proofs are given of the psychogenetic nature of the psychoneuroses: (1) in many of these disorders no physical cause can be found; (2) they are commonly precipitated by purely psychological experiences; (3) they can be cured by psychical means alone; (4) they can all be produced artificially by suggestion. It will be observed that in the first three of these proofs, if physical is written for psychological or psychical and vice versa, propositions result which contain as much truth as the originals. The fourth proof could be disputed on other grounds.

Dr. Hadfield's book is written from a one-sided point of view, but it is readable and lucid. A commendable effort is made to restrict the amount of jargon, in which the majority of works on psychodynamics abound.

Delinquency and Human Nature. By D. H. Stott. 1950. Dunfermline, Fife: Carnegie United Kingdom Trust. Pp. viii+460. Price 5*s*.

This is a report on an investigation into 102 delinquent youths. The author lived for the time required by the study in an approved school, and worked as a member of the staff. He was able to spend as much time with the lads as he wished, and to get to know them very well; and he could also interview the parents and was given access to official information. He chose to devote all his attention to an intensive study of the personalities and backgrounds of his subjects, and, on theoretical grounds which do not appear adequate, rejected the notion of studying any control group for comparison. As he makes clear in his first chapter, he is very critical of the standard methods of applying statistical techniques to work of this kind, and regards them as useless for the discovery of causes. His viewpoint is individual in other respects. He regards the constitutional differences between human beings as of little importance and of even less interest; investigation along constitutional lines is thought to be heuristically without value. "The main and indubitably innate characteristics of a species (and by this I mean, for man, the shape of his limbs, the structure of his brain, etc.) only vary, apart from mutations, within fairly narrow limits." From this it follows that the causes of differences in behaviour must be sought, almost exclusively, in past experiences.

In his clinical work with his subjects, the author shows sympathy, subtlety, and insight. As far as possible none of the findings are left uninterpreted. The extent to which the interpretations are found convincing, however, will depend on the viewpoint of the reader. Owing to his rejection of control studies, there is no evidence available to show whether they are right or wrong. Some of them seem very plausible; but it is left open for one to wonder whether he would not have found the same "avoidance reactions" and "mother-fixations" in neurotic, psychotic, or normal lads—and whether another investigator might not have found quite different explanations of abnormalities of behaviour, if he had been set to study Mr. Stott's subjects. The way in which interpretations are made which could equally well be true or untrue, may be illustrated by a single sentence: "Also, during this period Bligh's hand was badly scalded, which must have seemed an additional act of cruelty on the part of the harsh grandmother".

In an interesting appendix Mr. Stott relates his work on delinquency with a general theory of human behaviour. Its prime motivations are seen on the one hand in a disposition "to establish, more or less continuously throughout life, a relationship of fellow-feeling with some other person or people", on the other hand in a disposition towards self-realization, which "takes the form of a desire to count for something, to gain recognition, to operate effectively within the environment and not to be pushed hither and thither by external forces". The withdrawal reaction can then be seen as biologically necessary, to allow the individual to change his goal from persons or circumstances which have proved unpropitious; and the reaction itself can be envisaged as corresponding, neurologically, to a temporary phase of inhibition. The generality of this formulation is an obvious improvement on a number of rival theories in psychodynamics.

The Diagnosis of Hysteria. By D. W. Abse, M.D., B.Sc., D.P.M. 1950. Bristol: John Wright and Sons; London: Simpkin Marshall Ltd. Pp. 112. Price 8*s*. 6*d*.

This is an essay on the clinical manifestations of hysteria

based on the author's experiences as an army psychiatrist in India. The medical student and the general practitioner, especially in India, will find much useful information in this little book. For the specialist, the comparison between hysterical manifestations observed in Europeans with those of non-Europeans is of interest. Among Indian soldiers the classical symptoms of the *grande hystérie* were extremely frequent. They yielded to simple therapeutic measures much more readily than the more complex symptoms of the Europeans. The author's orientation concerning the causation of hysteria is broadly psychoanalytical.

Freud or Jung. By Edward Glover. 1950. London : Allen & Unwin. Pp. 207. Price 15*s*.

This is a work of destructive criticism. Dr. Glover's opinion that Jung's views were schismatic and false was formed 20 years ago, and in this book he does not pretend to be disinterested : he wants to supply students of psychoanalysis with a reasoned statement of what exactly is wrong with a system, like Jung's, which is in opposition to Freudian principles. He does this very effectively, if it be accepted that " wrongness " and opposition to Freudian principles amount to the same thing. Dr. Glover's skill in exposition makes it possible to follow, though not always to agree with the rather difficult argument, in which he contrasts Freud's with Jung's theoretical position. Readers who are not adherents of Jung will appreciate the gusto with which he has turned the latter chapters—on sociology, politics and alchemy, religion, and art—into lively exercises in denigration, for which Jung has supplied him with rather too much material. Impartial students of psychological systems might well conclude from this book and the current literature that no credence can be given to the comforting assurances, often stated by public relations officers of psychotherapy, that medical psychologists are now agreed on main principles.

Freud : Dictionary of Psycho-analysis. Edited by Mandor Fador and Frank Gaynor. 1950. New York : The Philosophical Library Inc. Pp. 208. Price $3.75.

The title of this work is a misnomer. It is not a dictionary but something between a glossary and a collection of Freudian aphorisms. Many words are listed which have no special psychoanalytic meaning, and Freud's views on them are quoted. Communism, telepathy, and *Weltanschauung* are thus included ; though neither under this last heading, nor under " Science " is mentioned Freud's statement that psychoanalysis includes itself in the general scientific *Weltanschauung* and attempts no special one of its own. Some words which are used in a special sense by Freud are, however, not included.

It is difficult to see what use this book will fulfil. Freud has himself clearly presented the essentials of the subject in his two volumes of " Introductory Lectures ", and the uninstructed, whether layman or medical, will gain far more by reading these, or perhaps even better " The Interpretation of Dreams " in all of which the concepts and phrases used are clearly defined. The present work may perhaps allow the drawing-room dilettante to converse with some apparent knowledge amongst the ignorant—a function which the trend of psychiatry in present-day America may encourage. The serious student of the subject may find that these brief excerpts will lead him to renew his acquaintance with the easy lucidity of Freud's more extensive writing ; and this is likely to be the book's main value. Dr. Theodore Reik in a prefatory nostalgic *laudatio temporis actae* seems to deplore any change in psychoanalytic teaching. Others may feel, however, that Freud would himself welcome growth and development in the science that he founded.

Psycho-Analysis. A Handbook for Medical Practitioners and Students of Comparative Psychology. By Edward Glover, M.D. 1949. London : Staples Press. Pp. 367. Price 15*s*.

Dr. Glover in this second edition, expresses his belief that few extensions of psychoanalysis have been made during the last ten years. He has therefore expanded his book, not because it was now out of date, but because it had previously suffered in places from over-condensation. Although there is now a rich supply of handbooks on psychoanalysis, this authoritative account is valuable, because of Dr. Glover's uncompromising adherence to Freudian orthodoxy, in the face of Kleinian, Alexandrian, Horneyan, and other deviations, and because of his ability to simplify and explain unfamiliar concepts without distorting them.

The Sexual Perversions and Abnormalities. A Study in the Psychology of Paraphilia. By Clifford Allen, M.D., M.R.C.P., D.P.M. 1950. Oxford University Press. London : Geoffrey Cumberlege. Pp. 346. Price 25*s*.

This is the second edition of a well-written and documented treatise. As in similar works, strange habits and distressing histories are reported in detail to illustrate the general statements in the text : it is a pity that in these the author has included some rather fulsome letters of gratitude that he received from patients who had benefited from his treatment. The lengthy chapter on therapy and prognosis errs somewhat on the side of optimism, but contains an informative account of the methods of treatment which the author employs : these include deep analysis, which he accelerates by allowing the patient " not only to say what he wishes in the consulting room but to do anything he wants to do also. This means that the fetishist is allowed to wrap himself in his mackintosh, the transvestist puts on his female clothes, the exhibitionist lies naked on the couch, and so on ". The reader concerned about " and so on " is reassured in the rest of the paragraph.

Sexual Deviations. By Louis S. London, M.D., and Frank Caprio, M.D., with foreword by Nolan D. C. Lewis, M.D. Washington, D.C. : Linacre Press. Pp. 702. Price $10.00.

The authors of this book are convinced that homo-

sexuality, exhibitionism, and other perversions are amenable to psychoanalytic treatment. The detailed case histories which make up the bulk of the book do not persuade the reader that such a belief is justified, except in a limited number of favourable cases. The case histories illustrate the variety of sexual deviations that can occur, and the experiences that have apparently brought about sexual aberration in these people, who are pathetic, revolting or interesting according to the reader's standpoint and his familiarity with the problem. The psychopathology is for the most part Freudian, but Stekel also is frequently quoted with approval. The writers say nothing about the social and cultural determinants of sexual deviation, though in a brief final chapter they deplore the present attitude of society towards sexual matters.

Fundamentals of Psycho-Analysis. By Franz Alexander, M.D. 1950. London: George Allen & Unwin. Pp. 312. Price 16*s*.

The author, who is one of the leading exponents of the integration of psychoanalysis with psychiatry and general medicine, gives in this book an excellent introduction to the theory and practice of psychoanalysis. His concepts differ in some respects from those taught in other psychoanalytic schools. He has never accepted the dualistic theory of instincts, while otherwise adhering to Freud's basic concepts. The far-reaching modifications of psychoanalytic theory proposed by a group of English analysts are not mentioned. In the therapeutic application of psychoanalysis the author's approach is unorthodox and extremely practical. He advocates the greatest possible flexibility of technique. The book illustrates the evolution which psychoanalytic theory and practice are undergoing in America.

Textbook of Neuro-Anatomy. By A. Kuntz, Ph.D., M.D. 1950. London: Baillière, Tindall and Cox. 5th Ed. Illustrated. Pp. 524. Price 61*s*. 6*d*. net.

In this textbook the author sets out "to give an orderly account of the fundamental anatomy of the human nervous system and sufficient physiological data to associate structure and function in a dynamic pattern". He aims to provide both student and physician with "a clear comprehensive presentation of the structural neural mechanisms and an adequate basis for the interpretation of their functional and clinical significance"; and the fact that his book has run into five editions is evidence of its value.

The text is accurate, conservatively up-to-date, interesting, and easy to read. Of the numerous illustrations, however, the best are those which have been borrowed from other sources. Those prepared especially for the book are in many cases too complicated and in almost every case grossly overlabelled. Furthermore, some of the 52 works cited in the appended list of "General Neurological Literature" are now out of date and could never have been regarded as classic. This list should either be revised and enlarged or omitted; as it stands, it serves no useful purpose. These criticisms, however, are of minor significance in relation to the excellence of the book as a whole, which can be highly recommended.

Essay on the Cerebral Cortex. By G. von Bonin. (American Lecture Series.) 1950. Oxford: Blackwell Scientific Publications Ltd. Illustrated. Pp. 168. Price 27*s*.

This is a scholarly and most helpful publication. It will be specially appreciated by neurologists and psychologists who often drop behind in the struggle to keep up with current American research and thought on the functioning of the cerebral cortex.

Electrophysiological Technique. By C. J. Dickinson, B.A., B.Sc. 1950. London: Electronic Engineering. Illustrated. Pp. 141. Price 12*s*. 6*d*.

The last few years have been revolutionary ones in physiological practice: they have seen much mechanical stimulating and recording apparatus eclipsed by more flexible electronic devices. Sufficient experience of the new methods has now been gained for some measure of standardization to be profitable. Mr. Dickinson's timely book assumes some familiarity with electronics —the chapter on time bases, for example, would probably be unintelligible otherwise—and it will be found extremely useful as a recipe book for the laboratory. It describes amplifiers, stimulators, oscillographs, time bases, time markers, power packs and electromechanical transducers, giving tested networks with appropriate component values. A valuable chapter recommends a limited range of easily obtainable valves adequate to all the purposes of the book. Valve-base diagrams and a useful technical bibliography are provided. This laboratory handbook will be welcomed by all physiologists who are engaged in laboratory or clinical research.

Children with Mental and Physical Handicaps. By J. E. Wallace Wallin, Ph.D. 1950. London: Staples Press. Pp. 549. Price 42*s*.

This is a scholarly and conscientious book based on many years' experience with handicapped children. Though the author's account of clinical aspects necessarily suffers from his lack of a medical training, he provides a comprehensive review of mental deficiency and of the psychological—and especially the educational —problems of children with diseases of the nervous system. The first five chapters examine the concepts of mental defect, the relationship between it and mental disease, and the characteristics of the educationally backward "dull normal" child. The principles of classification according to psychological characteristics, educability and vocational competence, and the causes and pathology of defect occupy the next section, in which epilepsy receives special attention. The last six chapters are concerned with the effects of encephalitis, cerebral palsy, infantile paralysis, microcephaly, hydrocephalus, and syphilitic brain affections in children. A valuable feature of the book is the carefully selected list of references to recent articles drawn from a wide variety of specialist journals. For studies of the

pathology and the genetics of mental deficiency other works must be consulted, but this book is a trustworthy general guide to the present state of knowledge and the growing points in the field of mental deficiency and crippling.

The November (1950) Issue

The November (1950) issue contains the following papers:

Infantile Hemiplegia Treated by Removing One Cerebral Hemisphere. By Rowland A. Krynauw.

Society of British Neurological Surgeons: Symposium on the Results of Operations on Acoustic Neuromas. By Gilbert Horrax, H. Olivecrona, J. B. Pennybacker and H. Cairns, and D. W. C. Northfield.

Postoperative Intracranial Hypotension. By Jerzy Chorobski.

Electrical Activity of the Human Brain During Artificial Sleep. By B. D. Wyke.

Observations on Diaphragmatic Movement in Some Neurological Disorders. By P. K. Robinson, W. H. Mosberg, Jnr., and R. C. W. Lowe.

Familial Ataxia, Deaf-Mutism, and Muscular Wasting. By W. B. Matthews.

The Nailbed Capillaries in Disseminated Sclerosis. By J. H. D. Millar and D. G. F. Harriman.

Memory Studies in Electric Convulsion Therapy. By Moyra Williams.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1., price 7s. 6d.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Group Life: The Nature and Treatment of its Specific Conflicts. By Marshall C. Greco. 1950. New York: The Philosophical Library, Inc. Pp. 357. Price $4·75.

Plasma Clot Suture of Periphal Nerves and Nerve Roots.—Rationale and Technique—By I. M. Tarlov, M.D. 1950. Springfield, Ill. (U.S.A.): Charles C. Thomas; Oxford: Blackwell Scientific Publishers Ltd. 47 illustrations. Pp. 116. Price 40*s*.

The Neural Crest: Its Properties and Derivatives in the Light of Experimental Research. By Sven Hörstadius. 1950. Oxford University Press (London: Geoffrey Cumberlege). 46 line drawings. Pp. 111. Price 15*s*.

L'Hypno-Analyse dans les Etats Schizophréniques et l'Automatisme Mental. By René Bessière and Joseph Fusswerk. 1950. Paris: Masson et Cie. Pp. 252. Price Fr. Fr. 750.–

Introduction à la Psychochirurgie. By P. Puech, P. Guilly, and G.-C. Lairy-Bounes, with a Foreword by A. Baudouin. 1950. Paris: Masson et Cie. 13 illustrations. Pp. 166. Price Fr. Fr. 520.–

Méthodes Biologiques en Clinique Psychiatrique. By Jean Delay. 1950. Paris: Masson et Cie. 68 illustrations. Pp. 536. Price Fr. Fr. 2,000.–

Modern Abnormal Psychology: A Symposium. Edited by W. H. Mikesell. 1950. New York: The Philosophical Library, Inc. Pp. 880. Price $10·00.

Principles of General Psychopathology: An Interpretation of the Theoretical Foundations of Psychopathological Concepts. By Siegfried Fisher, M.D. 1950. New York: The Philosophical Library, Inc. Pp. 327. Price $4·75.

Das Autogene Training (Konzentrative Selbstentspannung). By Prof. J. H. Schultz. 1950. Stuttgart: Georg Thieme. 6th ed. 17 illustrations. Pp. 328. Price DM. 27.–

Brouwer Memorial Volume. By A. Biemond, J. J. G. Prick, and J. Drooglever Fortuyn. 1950. Amsterdam: F. Van Rossen (Publishers). 300 text figures. Pp. 476. Price Fl. 11·85.

Hirndurchblutungsstörungen: ihre Klinik und Arteriographische Diagnose. By A. Brobeil. 1950. Stuttgart: Georg Thieme. 84 illustrations. Pp. 264. Price DM. 45.–

Il Sistema Nervoso Studiato con una Nuova Technica. By Lea Rossi del Bo. 1950. Milan: Officina D'Arte Grafica A. Lucini. Memorial dedication. 88 illustrations. Pp. 56. No price stated.

Physiologie et Biologie du Système Nerveux Végétatif au Service de la Chirurgie. By H. Laborit, with a Foreword by Jean Gosset. 1950. Paris: G. Doin et Cie. Illustrated. Pp. 164. Price Fr. F. 620.–

Les Céphalées Vasculaires: Étude du Rôle des Vaisseaux cérébraux dans la Genèse des Céphalées. By Jacques Barbizet. 1950. Paris: G. Doin et Cie. Pp. 123. Price Fr. F. 500.–

Précis de Neuro-Psychiatrie Infantile. By Gilbert-Robin, with a Foreword by Prof. Heuyer. 1950. Paris: G. Doin et Cie. 2nd ed. revised. Pp. 416. Price Fr. F. 1,500.–

Précis de Neurologie. By Prof. L. Rimbaud, with a Foreword by Prof. Forgue. 1950. Paris: G. Doin et Cie. 5th ed. revised. 280 illustrations including colour plates. Pp. 1106. Price Fr. F. 3,500.–

What is Hypnosis. Studies in auto and hetero conditioning. By Andrew Salter, with a Foreword by E. B. S. Strauss, M.A., D.M., B.Ch. (Oxon), F.R.C.P. 1950. London: Rockliff Publishing Corporation Limited. Pp. 95. Price 8*s*. 6*d*.

El Psicodiagnóstico Miokinético: su Teoria y su Practica. By Cesar G. Coronel, with a Foreword by Emilio Mira y Lopez. 1950. Beunos Aires: "El Ateneo". Illustrated. Pp. 289. Price not stated.

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SUBACUTE CORTICAL CEREBELLAR DEGENERATION AND ITS RELATION TO CARCINOMA*

BY

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Since Casper (1929) published a case of subacute cortical cerebellar degeneration associated with carcinoma, a number of cases with a similar association has been recorded. In the earlier cases (Parker and Kernohan, 1933 ; Greenfield, 1934) little or no comment was made on the association, but as more cases were reported it became evident that carcinoma played some part either in the aetiology or at least in the tempo of the nervous disease. It is however clear that not all cases of subacute cortical cerebellar degeneration are associated with carcinoma. It may therefore be useful to consider how common this association is, and what role carcinoma plays in causing or hastening the cortical cerebellar degeneration.

We have been able to collect from the literature only eight cases of cortical cerebellar degeneration in which the disease ran its course from onset to death in under 12 months, and are able to add four new cases in three of which there was also carcinoma. Even adding five additional non-familial cases in which the duration of the disease was under, or slightly over two years, the group is still a very small one but, although of no value for statistical study, its survey may throw light on the question of the relationship of the cerebellar disease to carcinoma.

It is probable that only a small proportion of the cases which fall in this group are recorded ; only so is it possible to explain the silence of the American literature on the subject since the early case report of Parker and Kernohan (1933). No doubt also symptoms of cerebellar disease are apt to be attributed to metastases when they appear in bed-ridden patients dying of carcinoma. The paucity of recorded cases, whatever its cause, is unfortunate since our knowledge of the aetiology and pathogenesis of cortical cerebellar degeneration is so slight that any addition to our knowledge, however indirect it may appear to be, is of value.

As it is notoriously difficult to distinguish clinically between the various forms of cerebellar degeneration or even to distinguish them from spinal cases of Friedreich type, we have confined our survey to cases in which a necropsy examination of the cerebellum has been made.

Case Reports

Case 1.—Mrs. J. B., aged 61, was admitted to Chase Farm Hospital on June 6, 1945, under Dr. Russell Brain, and died there on July 17 of the same year. Her history was that two months before admission she had felt weak and ill, had lost interest in her housework, and had had unpleasant, confused dreams. Soon after this her gait became unsteady, both legs being affected, but she did not fall. Her gait became progressively worse. Two weeks before admission she complained that her vision was blurred and there was occasional diplopia, and soon after this she had difficulty with her speech ; there was some difficulty in finding the right word, and her diction became indistinct. She also suffered from excessive salivation. During all this time she had generalized headaches, and cramp-like pains in the legs which kept her awake at night.

When examined at Chase Farm Hospital she was a spare, middle-aged woman, whose speech showed a combination of dysarthria and aphasia ; there was some alexia for long words ; no mental impairment was evident at this time. Her vision was good, and her visual fields full. There was no papilloedema. Nystagmus was present on lateral deviation of the eyes. It was rather slow on looking to the right and slower and less well sustained to the left. On looking upwards there were occasional nystagmoid jerks. No limitation of the external ocular movements was found. The left side of the palate rose rather further than the right

* Much of the subject matter of this paper formed part of the Hughlings Jackson Lecture given at the Neurological Institute, Montreal, in September, 1950, by J. Godwin Greenfield.

on phonation and the tongue was protruded to the right of the midline. No other evidence of cranial nerve involvement was found.

There was no evident weakness or modification of tone in the limbs but some ataxia was present, more in the legs than in the arms, and least in the right arm. Dysdiadokokinesis was also more evident in the left arm than the right. The gait was very unsteady ; she could not walk along a straight line ; but there was no true Rombergism. The deep reflexes were rather exaggerated in the arms, especially the left, the knee jerks were normal and the ankle jerks rather feeble. No abdominal reflexes were obtained. The plantar reflexes were flexor in type. No disturbance of the sensory system was found.

A lumbar puncture was done on June 7 and colourless cerebrospinal fluid was obtained. It contained 48 lymphocytes per c.mm., 100 mg. protein per 100 ml. with positive globulin reactions. The Lange gold sol gave a strong paretic reaction, 5555421100. The Wassermann reaction was negative in blood and cerebrospinal fluid.

The clinical condition taken in conjunction with the findings in the cerebrospinal fluid made the diagnosis of subacute spino-cerebellar degeneration reasonably certain. During her stay in hospital there was progressive mental deterioration and dysarthria so that her speech became almost unintelligible. She was unable to sit up owing to giddiness. She lapsed into coma on July 13 and died on July 17 about three and a half months after the onset of her illness.

Necropsy Report.—A post-mortem examination was made by Dr. Greenfield 16 hours after death. The only external evidence of disease was a scar in the right iliac fossa. Examination of the organs of the body cavity showed the right lung slightly adherent by purulent lymph to the chest wall over the upper part of the right lower lobe. The upper lobe and the upper part of the lower lobe of the right lung were in a condition of diffuse bronchopneumonia. The left lung was oedematous throughout with atrophic emphysema. In the heart there was slight patency of the foramen ovale, and the wall was rather thin and brown. The stomach and liver were healthy ; the lower coils of the small intestine were matted together by adhesions and there was some kinking of the ascending colon ; the rest of the colon was normal, the appendix being present. The uterus contained a small central fibroid, the wall being otherwise thin. In the right ovary there were two soft masses of carcinoma, each the size of a cherry ; one was degenerated in its centre. Masses of enlarged glands lay in the right iliac fossa and along the aorta, chiefly in front and at its sides. They were firm and white on section. The whole mass with the abdominal aorta weighed 450 g. A few small firm white glands were present also in the mesentery.

Histologically the tumour in the ovary and glands consisted of a number of small rounded collections of cells resembling collapsed acini, but seldom having a lumen. These small cell groups were separated from one another by very fine collagenous strands, and rather thicker collagenous septa divided the tumour into larger irregularly rounded masses. In most places the tumour cells were cuboidal with a fairly large, slightly granular cell body and irregularly rounded hyperchromic nucleus. In a few places they were more columnar and arranged in palisades along a basement membrane. Many larger multinucleated cells were also present, and in many of these the nucleus was imperfectly divided. Mitoses were fairly numerous. In some of the glands there was central necrosis of the larger groups of cells. In the Fallopian tube the arrangement of cells in small groups was lost, the cell bodies were more irregular in size and generally smaller, but a few acinar arrangements were seen here also. The thyroid gland presented a remarkable degree of lymphocytic infiltration with considerable swelling of the acinar epithelial cells, but less destruction of parenchymal tissue and less fibrosis than is usual in Riedel's struma. Many acini were normal, but many were small with irregularly swollen epithelium and very little colloid, and all gradations between these were seen.

The brain and spinal cord were removed and fixed entire in 15% formol-saline solution. The only naked eye abnormality was that the cerebellar folia were rather better demarcated than normal. The brain and cerebellum were both shrunken, the brain entire weighing 1,150 g. and the pons, cerebellum, and medulla 150 g. Frozen sections in the transverse plane were made at various levels of the spinal cord, medulla, pons and midbrain, and similar sections of the cerebellum in the sagittal and parasagittal planes and of the basal ganglia in the coronal plane. These were stained by haematein and Scharlach R for early myelin degeneration. Those from the cerebellum, medulla, and spinal cord were also stained by the Da Fano-Bielschowsky technique. Thin slices from neighbouring areas of the cord and brain stem, but not of the cerebellum, were treated by the Marchi-Busch (iodate-osmic acid) technique. Sections were also made after celloidin embedding from similar areas and from several areas of the cerebral cortex.

In the lumbar cord there was early Marchi degeneration in the pyramidal tracts which also showed itself in Scharlach R sections as irregular granular masses of lipid replacing some of the myelin rings. These took a rather redder stain than the surrounding myelin sheaths and were less anisotropic, but were not brightly sudanophilic. There was, both at this and higher levels of the spinal cord, some excess of lipochrome in the larger nerve cells.

At the thoracic level degeneration in a more advanced stage was seen in the direct spino-cerebellar tracts. Here the lipid was brightly sudanophilic and most of it was collected in large fat-granule cells. A zone of sudanophilic lipid was also seen round some of the small vessels.

In the cervical enlargement this degeneration involved a larger area on the lateral surface of the cord and on one side extended as far anteriorly as the posterior margin of the ventral horn. It was not however evident in sections stained by the Weigert-Pal technique.

In sections at the lower levels of the medulla, below the fourth ventricle the degeneration in the dorsal spino-cerebellar tract was very evident with Scharlach

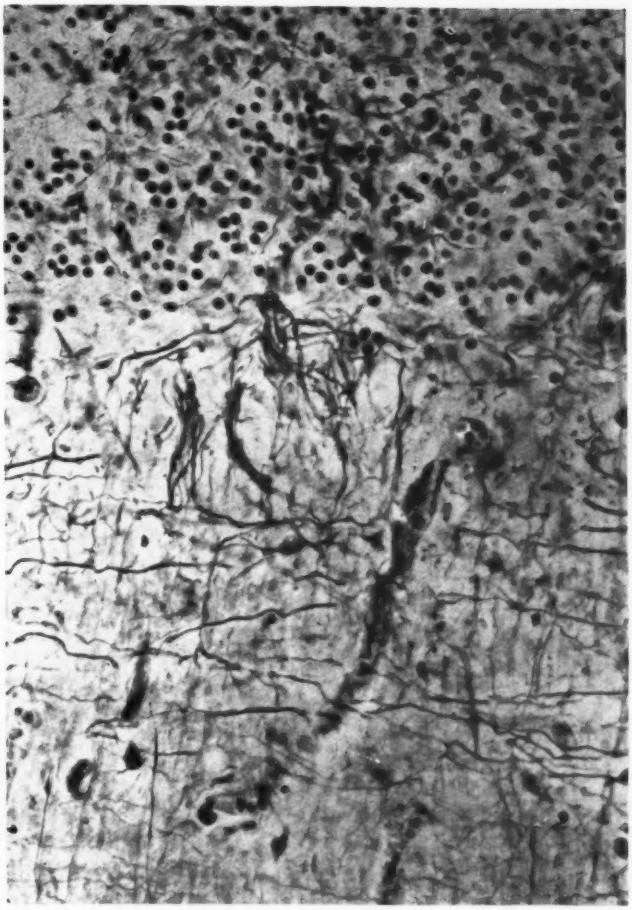

FIG. 1

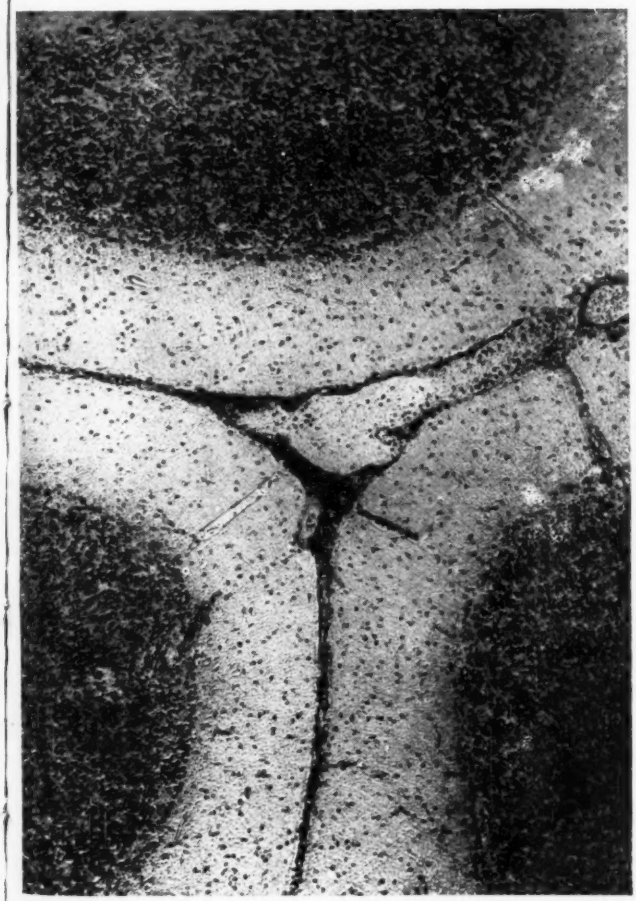

FIG. 2

FIG. 1.—Cortex of cerebellar vermis (Case 1) stained by Bielschowsky's method, showing loss of Purkinje cells with preservation of baskets and tangential fibres. The granule cells are rather sparse.

FIG. 2.—Cerebellar cortex (Case 1) stained with haematoxylin, showing widespread loss of Purkinje cells and lymphocytic infiltration of the meninges.

staining, but in the pyramidal tracts only an occasional fibre showed the earliest sudanophil change. The degeneration of these tracts therefore appeared to increase and to be older as they passed further from their cells of origin.

No degeneration was seen either with the Marchi-Busch or Scharlach R technique above the level of the medulla. The superior cerebellar peduncles and the strio-Luysial fibres which were degenerated in the cases of subacute-spino-cerebellar degeneration reported in 1934 by Greenfield showed no lesions in this case.

The most striking change in the cerebellum was an almost complete disappearance of Purkinje cells. This Purkinje cell loss was evenly distributed throughout the folia and convolutions, and was associated with the presence of powdery or rather more coarsely granular sudanophil lipid, chiefly extracellular, concentrated along the line of junction of the molecular and granular layers, and spreading out to a variable degree into the inner third of the molecular layer. There were also small accumulations of lipid granules in the granular layer and white matter, where they tended to be collected in microglial phagocytes. In the white centres of some folia, both in the vermis and hemispheres, as well as in the neighbourhood of the nucleus dentatus, quite large rounded fat granule cells had formed. A slight diffuse hyperplasia of microglia was present in the molecular layer. It did not anywhere take the character of glial bushwork. There was a slight loss of granule cells in some of the folia in all parts of the cerebellum, rather more widespread in the vermis than the hemispheres, but it was quite overshadowed by the wholesale loss of Purkinje cells.

In sections stained by Bielschowsky's method, the tangential fibres and baskets were well preserved, the latter being almost all quite empty, only a very few containing degenerated remains of Purkinje cells. Owing to the disappearance of the great majority of these cells very few "torpedoes" were found in the granular layer.

Celloidin sections added little to the evidences of degeneration given by frozen sections, but several points were more clearly brought out. In the spinal cord at all levels many vessels were cuffed with lymphocytes; these were not confined to the degenerated tracts but were common in the grey horns. The infiltrations were less numerous and thinner in the lumbar than in the cervical region. Perivascular infiltrations of meningeal vessels which were scanty and sparse in the lumbar region became more severe in the cervical, and here there was also some more diffuse meningeal infiltration. In addition there were occasional glial stars in the lateral columns, especially in relation to Clarke's column. In the medulla also fairly heavy infiltrations were seen under the floor of the ventricle and round the laterally emerging vessels. Some rather loose glial stars were seen in the nuclei of the dorsal columns. In the pons and midbrain perivascular infiltrations were quite sparse and slight and scarcely exceeded those often seen in normal brain stems. No loss of nerve cells nor gliosis was found in the inferior olives.

In the cerebellum perivascular infiltration was most evident round the meningeal vessels in the sulci, but many veins also in the white matter had a single or double cuff of lymphocytes round them. There was a general narrowing of the molecular layer with a moderate degree of isomorphous gliosis in it, associated with an increase in the number of Bergmann astrocytes. In sections stained by toluidin blue it was very difficult to find any Purkinje cells. Only an occasional shrunken cell, devoid of Nissl granules, could be found in any area. Perivascular infiltrations were abundant round the roof nuclei and present, though more sparsely, round the nucleus dentatus.

No evidence of degeneration could be found in the basal ganglia or cortex.

Summary of Case 1.—A woman of 61 began to feel weak and ill at the beginning of April. Her gait became unsteady and her vision blurred with occasional diplopia. She also suffered from cramp-like pains in the limbs which kept her awake at night. There was severe dysarthria and some aphasia and alexia. Nystagmus or lateral deviation of the eyes and slight weakness of the right side of the palate and tongue were found on examination. No sensory disturbance was found. The cerebro-spinal fluid contained 48 lymphocytes and 100mg. protein per 100 ml. and gave a strong paretic Lange curve. There was progressive physical and mental deterioration and she died on July 17, three and a half months after the onset of symptoms.

Post-mortem examination disclosed an unsuspected carcinoma of the ovary with secondaries in the pelvic and para-aortic lymph nodes, but no intracranial deposits.

Examination of the brain and spinal cord showed (1) diffuse almost complete disappearance of Purkinje cells, (2) degeneration of the direct spino-cerebellar tract and more recent degeneration of the pyramidal tracts in the lower levels of the spinal cord, and (3) perivascular and meningeal infiltration with lymphocytes in the cerebellum, medulla, and spinal cord.

Case 2.—P.W.K., aged 48, a schoolmaster, was admitted to Chase Farm Hospital under Dr. George Riddoch on November 4, 1939, and died there on December 2 of that year. The history of illness, as obtained from his wife, went back to May, 1939, when he found that he was much more erratic than formerly at lawn tennis. Otherwise he remained well till August, 1939, when he began to walk unsteadily, often bumping into his wife when he walked with her. Usually he veered to the right. He also began to drive his car badly, steering too near other vehicles as he passed them and always hitting the kerb when he pulled up. He consulted an oculist about this, and had glasses prescribed for him, but he did not himself feel that much was wrong, and was angry with his wife because she was afraid to go with him when he was driving. By September 1 he was staggering and walking like a drunken man. Owing

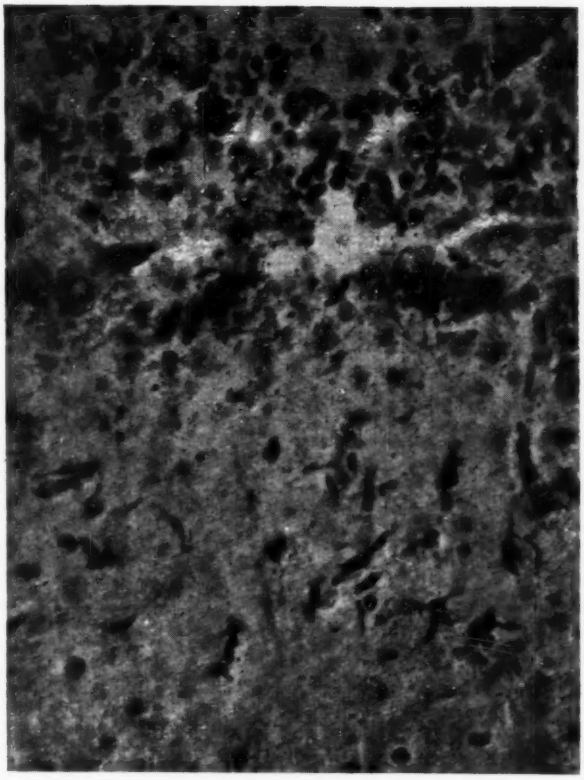

FIG. 3.—Cortex of cerebellar vermis (Case 1) stained with Scharlach R. and haematoxylin, showing microglial cells containing fat in the molecular layer. There are also fine sudanophil granules between the molecular and granular layers.

FIG. 5.—The cortex of the vermis of cerebellum (Case 2) stained by Bielschowsky's method, showing shrinkage of Purkinje cells and a " torpedo " on the axon of one of these cells.

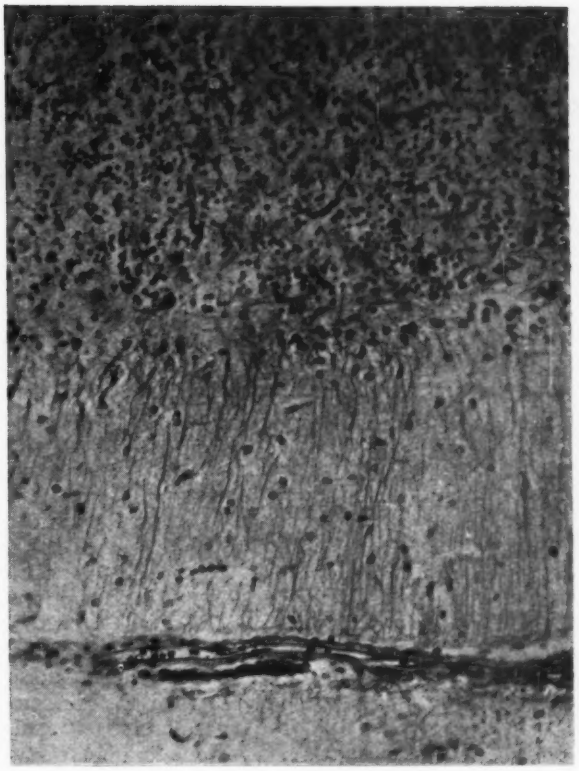

FIG. 4.—Cortex of the cerebellar vermis (Case 1) stained by Mallory's phosphotungstic acid haematoxylin showing isomorphous gliosis of the molecular layer and some sparseness of the granule cells.

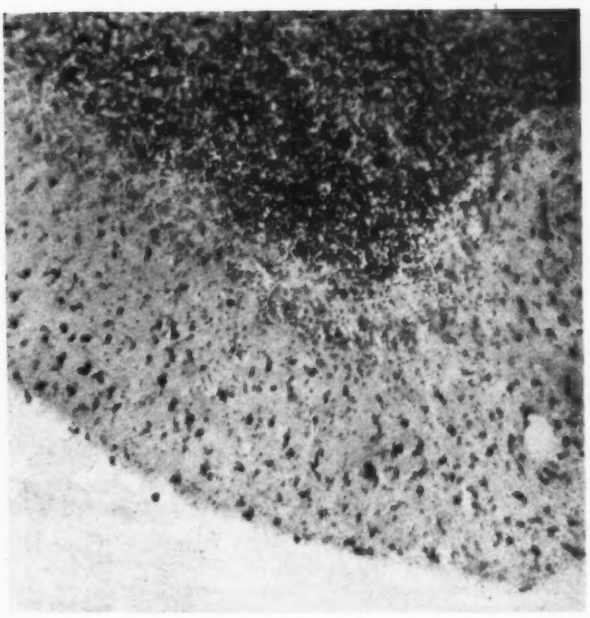

FIG. 6.—The cortex of the vermis of cerebellum (Case 2) stained by Scharlach R. and haematoxylin showing fatty granules collected within microglial phagocytes in the molecular layer.

to the outbreak of war he had to evacuate his school to the country and he managed all the arrangements for this without difficulty. During the second week in September, however, he began to show evidence of mental deterioration, especially of loss of memory. His walking became progressively worse, and he fell several times, but did not hurt himself.

His arms also had become clumsy, so that he tended to knock his cup over when he put it down. For the last two weeks before he was admitted to hospital he seemed to be living in the past ; he thought that he was at his old home with his parents, brothers, and sisters, and asked where his mother was, though she had been dead for eight years. He now began to realize that he was not well and that his mental faculties had deteriorated.

About the middle of September he had complained of double vision for short periods at a time, and in the last week of October this had become constant but varying in degree. The objects sometimes appeared alongside one another and occasionally one above the other, the higher being to the left. He also complained of roaring noises, like aeroplanes, and ringing noises like bells. During October his speech had become steadily more indistinct and he tended to repeat words, trying to speak them more clearly. He had had several giddy attacks in which his body seemed to rotate in a clockwise direction for about 10 minutes. They did not cause vomiting. He had learned Arabic and Hindustani during the 1914–18 war and, according to his wife, had recently talked to himself in these languages, though he had not spoken them for many years, and appeared to have forgotten them. He had become more particular as to cleanliness and neatness in his personal habits than he was before.

There had been no libido for six years. He had had venereal disease (? gonorrhoea) when in the Army in India. This had been treated by injections and there had been no recurrence. He also had had malaria in India. He had had a nervous breakdown with insomnia and loss of appetite 15 years before but had recovered after three months. He had symptoms of duodenal ulcer four years before but these had also cleared up. He smoked 20 cigarettes a day ; he drank alcohol only occasionally.

On examination it was noted that his memory was worse for recent than for past events. He was attentive and cooperative and could calculate well and had fair insight into his disability. He did not know the date, and thought that George V was still alive, but had a hazy recollection of the Duke of Windsor coming to the throne. He did not know the capital of Poland nor that of the U.S.A. and could not recall what he had read recently. There was a moderate degree of dysarthria, the speech being ataxic and slightly slurred. Examination of the cranial nerves showed a slight left sided ptosis with a convergent strabismus owing to weakness of the left external rectus muscle. There was fine nystagmus on extreme deviation to the right and left, equal on the two sides, but no vertical nystagmus. The pupils were eccentric, lying slightly to the nasal side in both eyes, symmetrically. They reacted well to light and sluggishly on accommodation. The palate deviated slightly to the right on phonation.

The upper limbs were hypotonic, especially the left. The fingers of the left hand were held out of alignment and there was fine tremor in the fingers of the right hand and slight rotatory tremor of the left arm. In purposive movements there was marked ataxia with intention tremor greater in the left arm than the right, and rapid alternating movements were performed poorly, especially with the left arm. The legs also were hypotonic and ataxic, more on the left side than the right, but there was no weakness or wasting. The deep reflexes were all rather sluggish. The abdominal reflexes were present and the plantars of flexor type. No loss of cutaneous sensibility was found. His gait was grossly ataxic. He walked on a wide base with his arms hanging limply by his side and the head held rigidly. The left leg was dragged slightly. He deviated more to the left than the right when walking, and tended to fall backwards and to the left when standing with heels and toes together. His unsteadiness was not increased when he shut his eyes.

Apart from the fact that the upper part of the chest moved better on the right side than the left, there was no evidence of disease of the thoracic or abdominal organs. The blood pressure was 130/100 mm. Hg.

A lumbar puncture was performed on November 5, 1939. The pressure was normal. The fluid contained 1 cell per c.mm. and 40 mg. protein per 100 ml. The Lange and Wassermann reactions were normal.

By November 20 the dementia had progressed considerably. The patient was drowsy and did not now speak unless spoken to, but he cooperated fairly well. There was occasional urinary incontinence.

The left pupil was larger than the right ; both reacted well. There were bilateral ptosis, greater on the left side, paralysis of convergence and defective conjugate movements of the eyes to right and left, upwards and downwards. On this examination nystagmus could not be elicited. There was no change in the physical signs in the trunk or limbs, and no evidence of involvement of the pyramidal tract.

The dementia progressed rapidly and he died on December 2 about seven months after the onset of symptoms.

Necropsy Report.—A post-mortem examination limited to the brain and spinal cord was made 36 hours after death. The skull was rather thin with some roughening of the inner surface. The spinal laminae were softer than normal. The sulci of the brain were rather wide and the cerebellar folia unusually distinct, especially in the vermis. The brain weighed 1,625 g.

After fixation in 10% formol saline solution frozen and celloidin sections were made of various areas of the cerebral cortex ; sections in the mid- and parasagittal planes were made of the cerebellar vermis and hemispheres and transverse sections of the brain stem and spinal cord.

Frozen sections stained by Sudan IV and haemalum showed no evidence of degeneration except in the cerebellum where it was greatest in the vermis. Here anisotropic lipid was scattered in considerable amounts,

mostly as intracellular accumulations in the molecular and granular layers. There was slight loss of Purkinje cells, and in sections stained by Bielschowsky's method numerous " torpedoes " were found on the axons of the Purkinje cells in the granular layer. These were more numerous in the vermis than the lateral lobes. There was also in the vermis considerable loss of baskets round the Purkinje cells ; some had none, and round others the fibres were scanty. In the lateral lobes no loss of basket fibres was seen. In celloidin sections stained with toluidin blue and with iron haematoxylin, with van Gieson, and with Mallory's phosphotungstic acid haematoxylin, more severe changes were seen in the vermis than in the lateral lobes. Although there was no great loss of Purkinje cells, most of those in the vermis were shrunken and appeared as narrow elongated cells lying among greatly proliferated nuclei of Bergmann astrocytes. The cells of the granular layer also appeared more sparse than normal. In frozen sections stained by Victoria blue a diffuse isomorphous gliosis was seen in the molecular layer. In the lateral lobes the proliferation of Bergmann astrocytes and the gliosis in the molecular layer were variable ; they were slight in most places and nowhere severe. A smaller proportion of Purkinje cells was shrunken and there was no definite loss of granule cells. The nucleus dentatus appeared normal and the inferior olives showed no loss of cells ; some surcharge of lipid was present in these cells but this was probably to be explained by the patient's age and terminal illness.

Sections of the cortex, basal ganglia, brain stem and spinal cord showed no abnormality.

Summary of Case 2.—A schoolmaster, aged 48, found at the beginning of May that he was much more erratic than formerly at lawn tennis. In August he became unsteady in his gait and drove his car badly ; in September his memory became worse and he saw double, at first for short periods at a time, but later more constantly. The ataxia of his arms and legs had now become much worse.

When examined at the beginning of November there were considerable loss of memory for the events of the past few years, moderate dysarthria, strabismus due to weakness of the left external rectus muscle, slight nystagmus on lateral deviation of the eyes to either side, ataxia of the arms and legs, and a reeling gait. The cerebrospinal fluid was normal. During his stay in hospital the dementia increased rapidly to a condition of subcoma in which he died on December 2, about seven months after the first symptoms were noted.

The evidence of disease was confined to the cerebellar cortex where there was some degeneration of Purkinje cells, showing itself as shrinkage of the cell body and the formation of torpedoes on the axons. Loss of basket and tangential fibres was also evident. These changes were greatest in the vermis. No degeneration of spinal tracts or lymphocytic infiltrations were found.

Comment.—It was unfortunate that no examination was made of the thoracico-abdominal viscera in this case. Although the course of the disease did not differ greatly, if at all, from that of other cases of subacute cerebellar degeneration, the normal cerebrospinal fluid and the absence of degeneration of spinal tracts and of perivascular infiltrations distinguish the case from the other three here described which have been associated with carcinoma. It is difficult to date the onset of symptoms in this case in relation to other cases, as the loss of accuracy at lawn tennis, which was the first symptom, was a much more delicate sign of cerebellar dysfunction than the first symptoms in the other cases. Unsteadiness of gait, of sufficient degree to be noticed by his wife, did not appear for a further three months and from that time until his death about four months later the downward course of the disease was rapid. But even if we date the onset as four months before death, giving the same duration of symptoms as in Case 1, the degree of damage to the cerebellum was very much less. Whereas in Case 1 there was almost complete loss of Purkinje cells, in Case 2 the loss was slight although many cells, especially in the vermis, were shrunken and degenerated. Here, as in many cases of early disease of the central nervous system, the most definite evidence of disease was the lipid katabolism, which appeared to involve chiefly the tangential fibres of the molecular layer.

Case 3.—Mrs. B. T., aged 54, was admitted to the Radcliffe Infirmary, Oxford, on January 19, 1945, under Mr. Pennybacker. The patient had been well till the end of October, 1944, although feeling rather tired after a frontal sinusitis which she developed in mid-October. At the beginning of November her husband noticed that she seemed to be " walking on air " and holding her arms out from her sides like a tight-rope walker. The next day her arms and legs were covered with a blotchy rash which lasted three days. After this she felt very tired. She burned her leg on a hot-water bottle without being aware of it, but there had been no noteworthy loss of sensation since, and it is not clear that this accident was due to loss of skin sensibility. She became weaker, and by Christmas Day, 1944, could only walk with her husband's support.

She attended hospital as an outpatient on January 3, 1945, and saw Mr. Pennybacker. On that evening her mind appeared to wander, and continued to do so, although she had lucid intervals. She was admitted to the Radcliffe Infirmary on January 19, 1945. On being questioned there she denied having had any diplopia, visual, auditory, or olfactory hallucinations. There had been no fits, paraesthesiae, or numbness ; for the last few months there had been urgency of micturition.

On examination she was a pale, restless woman, showing considerable dysarthria. She was rational one moment and talked nonsense the next, but there

was no nominal aphasia. Although she had difficulty in grasping objects, there was no evidence of astereognosis. She seemed to see fairly well and ophthalmoscopic examination revealed no abnormality. There was spontaneous nystagmus on convergence to the right with the slow component to the right. She was deaf in the right ear. Otherwise no evidence of involvement of the cranial nerves was found. In the upper limbs there was generalized wasting and corresponding weakness mostly in the thenar and first dorsal interosseous muscles. Tone was normal. There was some uncertainty in the finger nose test, more on the right than on the left side, and when she shut her eyes the finger missed the nose. Alternating rapid movements were performed with uncertainty. In the lower limbs there was generalized weakness but no dystonia. The legs were too weak to perform tests for coordination. The deep reflexes in the arms were normal ; the right knee jerk was absent, the left increased. The right ankle jerk was increased and the left normal. The right plantar was normal, the left doubtfully extensor. The abdominal reflexes were not obtained. There was no evident loss of superficial sensibility. Postural sensation was not impaired in the arms but the threshold was increased in the legs, and vibration sense was lost over the right ankle and diminished over the left ankle.

On January 20 lumbar puncture gave fluid with blood admixture at a pressure of 70 mm. It contained 60 leucocytes (18 polymorphonuclears, 42 lymphocytes) and 18,000 red cells per c.mm. and 140 mg. protein per 100 c.mm. (The polymorphonuclear cells and up to 10 lymphocytes were to be accounted for by the blood admixture.)

X-ray examination showed the shadow of the root of the right lung to be enlarged and of increased density. This appeared to arise from glandular masses in the right mediastinum.

The diagnosis of carcinoma involving the mediastinal glands, right temporal lobe, and cerebellum was made. On January 29 Mr. Pennybacker found skew deviation of the eyes on looking to the left along with some difficulty in maintaining conjugate deviation. There was ataxia of the limbs which was gross on the right but less on the left side. She had difficulty in passing urine and had to be catheterized.

A blood count on this date showed :

Hb.106%, platelets 360,000, leucocytes 6,000 per c.mm., neutrophils 56%, eosinophils 1%, lymphocytes 34%, monocytes 8%, Türck cells 1%.

A second lumbar puncture on the same day gave 7 c.mm. of very slightly yellow fluid, with 9 lymphocytes and 200 red cells per c.mm. ; protein 150 mg. per 100 c.mm. The Pandy reaction was strongly positive, and the Lange reaction gave a weak curve in paretic zone, 22211000.

She was transferred to Newbury District Hospital on February 3, 1945, and died there on or about February 15, the total duration of symptoms having thus been three and a half months.

At the post-mortem examination, which was made at the Newbury Hospital on Feburary 16, no carcinomatous deposits were found in the brain. The cerebellum and brain stem, already sliced in several places, a piece of lung showing carcinomatous invasion of the wall of a bronchus and of the surrounding alveoli, and two enlarged lymph nodes from the mediastinum were sent to Dr. Daniel. Section of the lung and lymph nodes showed an oat-celled bronchial carcinoma with secondary deposits in the lymph nodes which were largely necrotic.

Histology of the Cerebellum and Brain Stem.—Sections of the cerebellar cortex showed an almost complete loss of Purkinje cells, with preservation of the baskets, almost all of which were empty. Here and there three or four well-preserved Purkinje cells could be seen lying close together. There was also a very noticeable loss of granule cells, the layer as a whole being narrow and its cells sparse. Some of those that remained stained well ; others showed a faint, rather diffuse staining reaction and appeared to be degenerated. Moderate gliosis was seen both here and in the white matter where the most striking abnormality was cuffing of the small vessels with lymphocytes. Sections stained by Sudan IV (Scharlach R) showed early lipid degeneration in the granule cell layer and in the white matter, and numerous Marchi-stained lipid granules were present in the white matter.

There was a striking increase of Bergmann cells and fibres in the molecular layer with a microglial reaction which was both focal and diffuse. In the nucleus dentatus the cells were sparse and contained rather more lipochrome pigment than usual, and the astrocytes had rather prominent cell bodies with thick fibres passing from them. In this nucleus there were many clumps of proliferated microglial cells and some small round cells of indefinite origin. Cuffing of the vessel walls with lymphocytes was here well marked. In sections of the lower medulla slight collagenous thickening of the meninges and infiltration of these with lymphocytes was seen ; the perforating vessels, especially those of larger size, often showing well-marked lymphocytic cuffing. The cells of the inferior olive appeared to be diminished in number and contained some excess of lipochrome. Elsewhere the nerve cells appeared normal. In sections of the upper medulla the appearances were essentially similar. There was gliosis of the inferior olive, and many collections of microglial cells were seen in it ; some of them appeared to be perivascular and others to be formed round the remains of nerve cells, while others appeared to have no relation either to nerve cells or vessels. The walls of some of the subependymal vessels were thickened.

Frozen sections stained by Scharlach R showed Sudanophil lipid in the spino-cerebellar tracts, and rather earlier myelin changes in the dorsal columns at their termination in the nuclei gracilis and cuneatus. The katabolism of myelin as shown both by Scharlach R and Marchi staining was greatest in the direct cerebellar tracts.

Summary of Case 3.—A woman of 54 had not felt well since the end of October when she had had frontal sinusitis. Her gait then began to be ataxic and this became worse rapidly so that by Christmas

FIG. 7

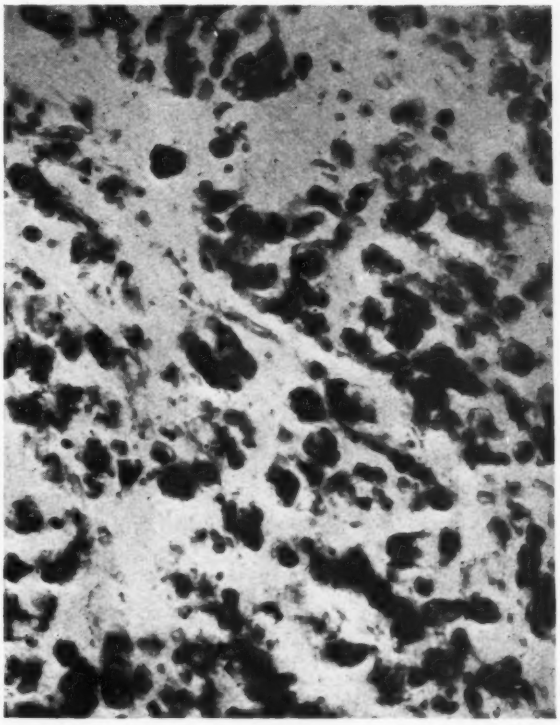

FIG. 8

FIG. 7.—Cortex of the cerebellar hemisphere (Case 3) stained by Bielschowsky's method showing empty baskets. In addition to the well-preserved fibres making up the baskets, tangential fibres are seen. Note the paucity of granule cells.

FIG. 8.—Direct spino-cerebellar tract (Case 3) in lower medulla stained Scharlach R and haematoxylin showing the degenerated sudanophil myelin as black masses.

FIG. 9.—Inferior olive (Case 3) stained Mallory's phosphotungstic acid haematoxylin. Two enlarged astrocytes, one of which is binucleated, are seen on either side of a nerve cell. There is a general increased density of the neuroglial fibre network.

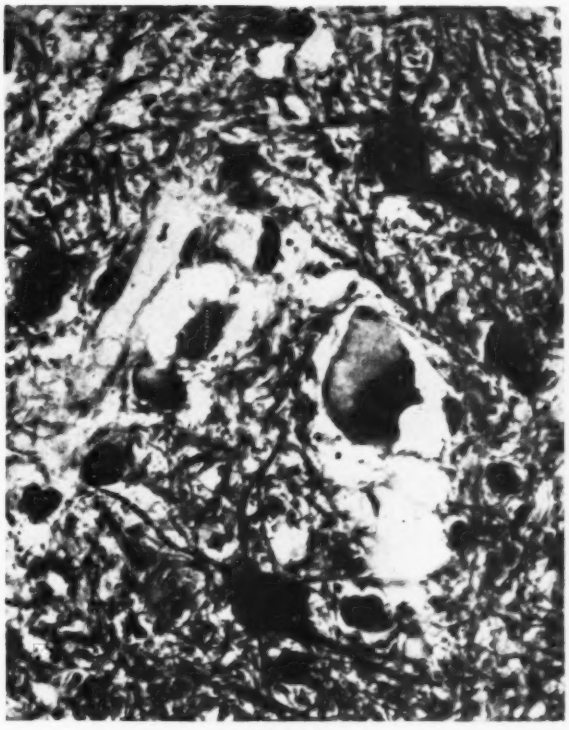

FIG. 9

she could only walk with support. Early in January mental confusion appeared, along with dysarthria, and ataxia of the arms. There were nystagmus on right lateral deviation, some deafness in the right ear, considerable weakness and some ataxia of the arms and great weakness of the legs. The right plantar response was doubtfully extensor in type. Radiographs showed enlargement of the hilar shadow in the right side of the chest, indicating carcinoma, primary or secondary, in that region. The cerebrospinal fluid on the first examination contained an excess of cells and protein, but the examination was vitiated by blood admixture. A second examination gave 9 lymphocytes per c.mm., 150 mg. protein per 100 ml., and a weak Lange curve in the paretic zone, 22211000. Skew deviation of the eyes on looking to the left and some failure to maintain conjugate deviation were present at this time. The patient died in the middle of February three and a half months after the onset of symptoms.

Post-mortem examination showed a bronchial carcinoma with involvement of the hilar lymph nodes.

The changes in the nervous system were similar to those in Case 1, namely, (1) practically complete loss of Purkinje cells with preservation of baskets; (2) degeneration of the direct spino-cerebellar tracts, and a less severe and more recent degeneration of the dorsal columns; (3) lymphocytic infiltrations and glial stars in the cerebellum and medulla.

Case 4.—A.C., a man aged 56, was admitted to the Radcliffe Infirmary, Oxford, under Mr. Pennybacker, on November 9, 1945, and died there on November 19. His history was that on demobilization from the army in June 1945, he had been medically examined and found perfectly fit. At this time he felt quite well, but one week later he, along with several of the men in his unit, had a sharp attack of diarrhoea and vomiting. On July 7, he went for a week's holiday to Blackpool and while there had aching pains in his knees and shins, such as he had had with malaria. This pain passed off in two days. On his return to work in the middle of July, he had severe indigestion with aching pains in the umbilical region and on the right side of the abdomen, coming on immediately after a meal. He was off work with this for three weeks, and at the end of that time was quite free from pain and felt well. On his return to work, however, he found that he was quite tired out by a full day's work, and he became progressively unsteady on his feet, until he was afraid of being dismissed for being drunk on duty. At that time he had pains in the lumbar region, calves and knees radiating up the thighs and down to the feet. These pains were exacerbated by exercise. He was also giddy in the sense that he felt as if he were drunk. Subsequently he had vertigo, especially if he turned his head suddenly. He gave up work, because of these symptoms, after seven weeks.

Early in October he noticed that his vision was blurred and he had periods of diplopia, the images being sometimes one above the other and sometimes side by side. On admission he could only read with a magnifying glass, with one eye closed. He had been in bed since the end of October.

His family history contained nothing of interest. His wife and three daughters aged 18, 8, and 5 years were well. His parents had died at advanced ages. One brother was well and another had died from wounds in the 1914–18 war. He had smoked fewer than 10 cigarettes a day and drank less than a pint of beer a week.

On examination he was an intelligent man, able to give a full history, and to cooperate well. He looked strong and well. The glands in the groins were palpable but not hard or tender.

Examination of the cranial nerves showed his vision when corrected to be 6/12R and 6/9L with full fields. There was bilateral papilloedema. Nystagmus was present in all positions of the eyes, slow and coarse to the left, rapid and fine to the right. The right pupil was larger than the left and reacted more briskly to light; both pupils contracted on accommodation-convergence. No other abnormalities of cranial nerve function were found. The upper limbs were hypotonic, but strong. Slight intention tremor was present in both arms in the finger-nose test, but no dysdiadokokinesis, or clumsiness on rapid alternating movements. In the lower limbs tone and power were normal, but there was slight incoordination in the right leg in the heel to knee test. The deep reflexes in the arms were rather weak on the left side, the right knee jerk was stronger than the left and the right ankle jerk weaker than the left. The abdominal reflexes were absent and the plantars doubtfully flexor in type. His gait was grossly ataxic with a wide base. He was unable to stand with his eyes open for more than a few seconds. Sensibility was normal over the body and limbs to all forms of stimulus. There was a large, left-sided hydrocele; examination of the thoracico-abdominal viscera showed no abnormality. His blood pressure was 135/90. It had been found to be 200/100 before his admission to the Radcliffe Infirmary. The pain in his back and legs had now almost disappeared. Lumbar puncture on November 12 gave faintly blood-stained fluid at a pressure of 260 mm. It contained 22 lymphocytes per c.mm. and 80 mg. protein per 100 ml. The Lange reaction was not performed.

As the symptoms and physical signs indicated a cerebellar neoplasm, subtentorial decompression was performed by Mr. Pennybacker on November 13, but the only abnormality found was thickening of the arachnoid which in places was adherent to the dura mater. The patient recovered well from the operation, but during the night of November 14 became restless, and by the next morning he had become cyanosed and semi-comatose with stertorous breathing. The wound was re-opened and a large haemorrhage was found passing into the cerebellum. This was removed as far as possible, and the patient's condition improved for

a time, but this improvement was not maintained and he died on November 19, four and a half months after the onset of symptoms.

A post-mortem examination was performed on the following day. The bronchi contained much mucopus. The upper and lower lobes of the right lung contained focal areas of pneumonic consolidation which were breaking down in some places. Elsewhere the lungs were congested. There were dense adhesions of the left lung to the diaphragm. The hilar lymph nodes were large, purple and fleshy. On section of the lungs after fixation, firm, greyish tissue was seen adjacent to the smaller bronchi in a number of places in the right upper lobe, but no ulceration of bronchi or clear evidence of tumour was found. The heart weighed 400 g., but was otherwise normal ; its vessels were in good condition. The suprarenal gland on either side contained a rounded soft homogeneous grey mass of tumour. This measured 2 cm. on the right side and was rather smaller on the left. No other tumour masses were found in the abdominal cavity. The prostate was soft with a few small areas resembling simple hyperplasia. There was a large hydrocele, with a cyst in the head of the epididymis, on the left side. The left testis appeared normal, the right atrophic and soft with a smaller hydrocele.

On histological examination the firm areas in the right lung consisted of infiltrations by an oat-celled carcinoma of bronchial type. The growths in the suprarenal and the infiltrations in the bronchial lymph nodes were of similar character.

Examination of the Central Nervous System.—The posterior parts of both cerebellar hemispheres were rather fragmented and haemorrhagic from operative trauma and the cisterna magna was filled with blood clot, as was also the ventricular system. Section of the brain after fixation showed slight ventricular dilatation, but no evidence of secondary deposits of tumour. In the cerebellum there was a recent operative cavity in the superior vermis and left cerebellar lobe, the adjacent tissue being studded with petechial haemorrhages. The spinal cord was, unfortunately, not examined, but as the brain was removed by approach from the back, several of the upper cervical segments were taken out along with the brain stem.

Histological Examination.—The meninges over the cerebellum were slightly thicker than normal and were infiltrated by lymphocytes, plasma cells, and some macrophages. Numerous red blood cells were also present. In the molecular layer of the cerebellum there was a slight diffuse increase of microglial nuclei, as well as many foci resembling glial " bush-work "; some of these lay round vessels. The Purkinje cells were lost over considerable stretches where the Bergmann astrocytes were proliferated, but the loss was much less than in Cases 1 and 3. The tangential fibres and basket fibres were preserved and there were many empty baskets. In most of the remaining Purkinje cells the Nissl granules were powdery, but in a few they were quite normal. The nuclei of the granular layer were decreased in number but those that remained appeared

FIG. 10.—Cerebellar cortex (Case 4) stained by haematoxylin showing microglial " bush " appearance (*gliastrauchwerk*) along the dendrites of a Purkinje cell which has degenerated. × 150.

normal. No " torpedoes " could be found in this layer. No loss of nerve cells was found in the nucleus dentatus, though there was a slight increase in lipochrome pigment in its neurons. The astrocytes here showed slight enlargement of the cell body and thickening of their fibres, and slight perivascular infiltration was also seen in this area.

In the medulla similar changes were seen in and around the inferior olives and in the restiform body, and some glial stars were also present in these areas. Sections stained by Scharlach R and haemalum showed in the cerebellum some granular stippling and small collections of lipid granules along the line of the Purkinje cells, and more sparsely among the granules. Very little sudanophil lipid was found in the centres of the folia, but the Marchi-Busch technique revealed some early degeneration here.

In the cervical cord fairly heavy infiltration of the meninges with lymphocytes and macrophages was present and the perforating vessels were cuffed with similar cells. A few glial stars were present in the grey matter. The direct spino-cerebellar tracts showed degeneration both with the Marchi-Busch technique and with Scharlach R, and early changes in the myelin of the dorsal columns were seen by the latter method.

No definite changes either with cell stains or with the Marchi-Busch technique were found in the pons or midbrain. In the putamen and caudate several of the medium sized veins were thrombosed and there was some lymphocytic infiltration of their walls as well as in those of veins under the walls of the ventricles. A few glial stars were also seen here. In the supra-optic nucleus there was a definite excess of microglial

nuclei, and some perivascular lymphocytic cuffing. Many of the nerve cells of this nucleus contained crystals of formol-haemoglobin pigment. A small focus of softening was present in the white matter of the occipital lobe and there was slight perivascular and meningeal infiltration in this region.

Summary of Case 4.—A previously healthy man of 56 began in July, 1945, to have aching pains in the legs for two days, and thereafter became rapidly weak so that he was very tired after a full day's work and walked like a drunken man. The pains in his legs returned and were made worse by exercise. He felt giddy when he turned his head suddenly. He had to give up work in October and at this time suffered from diplopia. On examination in hospital on November 9 there was bilateral papilloedema and nystagmus in all positions of the eyes. The upper limbs were hypotonic and slight intention tremor was present but no other evidence of cerebellar incoordination. In the lower limbs also incoordination was slight, but the gait was grossly ataxic with a wide base, and he was unable to stand steadily. The cerebrospinal fluid contained 22 lymphocytes per c.mm. and 80 mg. per 100 ml. of protein. The Lange reaction was not performed. The Wassermann reaction was negative. A subtentorial decompression operation was performed on November 13. This was followed by a reactionary haemorrhage into the cerebellum and the patient died six days later.

Necropsy.—The right lung, mediastinal lymph nodes and both suprarenals were invaded by an oat-celled bronchial carcinoma. No secondary growths were found in the brain or elsewhere in the body. On examination of the nervous system the most evident lesions were (1) loss of many Purkinje cells with preservation of baskets, and slight rarefaction of granule cells; (2) early degeneration of the direct cerebellar tracts and dorsal columns; and (3) lymphocytic cuffing in the cerebellum, medulla, and spinal cord.

Discussion

In these four cases symptoms of cerebellar disease developed fairly rapidly in subjects past middle age and contributed to their death at intervals of three and a half to seven months from the onset of the disease. Post-mortem examination showed diffuse degeneration of the cerebellar cortex and in three also degeneration of one or more of the long tracts of the spinal cord. In these three cases there was also carcinoma; of the lung in two and of the ovary in one. In two of the three cases carcinoma was unsuspected during life.

The relationship of this small subacute group to the larger group of cortical cerebellar degenerations has been recently discussed by Zülch (1948). He divides cortical cerebellar atrophies into five groups: (1) chronic cortical (grey) atrophy, affecting the vermis especially, which is an exaggeration of local ageing, without evident exogenous influence; (2) a group of cases with an acute course and apparently an extrinsic causation, especially neoplasm, many dying of the cancer rather than of cerebellar disease; (3) a group having an acute or sub-chronic course, coming on with acute general disease, e.g. enteritis, syphilis, tuberculosis or alcoholism, in which the cerebellar degeneration may cease to progress when the cause ceases to act, but may regress in later life; (4) a group in which cerebellar disease has been present from childhood but is progressive; (5) familial cases.

Zülch's second and third groups interest us here especially. While it is not clear what he means by the terms "acute" and "subchronic" he suggests that such forms of cerebellar disease are not rare. Yet we have been unable to find more than 12 cases in the literature in which the disease has run its course in less than a year, including the two recorded by Greenfield in 1934 and the four here recorded. The others were reported by Murri (1910), Schroeder and Kirschbaum (1928), Casper (1929), Zülch (1936), Alessi (1940), and Munch-Petersen (1947). In considering this subacute group it is convenient to add cases with a rather longer history, up to about two years, as they have many features in common with those which prove fatal under a year from the onset. Such cases were recorded by Parker and Kernohan (1933) 27 months, Kennard (1935), 18 months, Zülch (1936), 19 months, and Brouwer and Schlesinger (1947), $14\frac{1}{2}$ months. Thus 16 subacute cases in all will be considered in this discussion. The subacute cases reported by Akelaitis (1938) have not been included here as they belong to the familial group of cerebello-olivary degeneration, but in them, as in three of our present cases and five of the previously recorded cases, there were also symptoms of mental disease.

Clinical.—This subacute group is characterized clinically by the rapid appearance of cerebellar symptoms. Unsteadiness of gait is usually the first or a very early symptom and is followed later by clumsiness of the hands and dysarthric speech. After a few weeks or months the incoordination becomes so severe that the patient is no longer able to sit up unsupported. A less usual early symptom of cerebellar disease is diplopia, which was present in all the four cases here recorded. In three it was a fairly early symptom and had been present before

admission to hospital, while in Case 3 it was only noted, along with skew deviation of the eyes, on examination in hospital. This symptom is well recognized as an early sign of cerebellar tumour, and attention has been drawn by two of us to its occurrence during the earlier phases of subacute cerebellar disease of demyelinating character in young children (Brain and Greenfield, 1950). Its occurrence in cortical cerebellar degeneration is not so unusual as textbook descriptions of the disease would suggest. It was an early symptom in the cases reported by Casper and Kennard and in one of those reported by Zülch. In most of these cases the diplopia varied from time to time and appears to have been due to lack of balance rather than to paralysis of eye muscles.

Nystagmus appears to be more common in subacute than in chronic cases of cortical cerebellar degeneration. In their classical paper on this condition Parker and Kernohan say that there are rarely more than a few unsustained jerks of the eyes on lateral deviation. However, definite nystagmus was present in the four cases recorded here, as well as in six of the other twelve cases under review.

Pains in the legs were an early symptom in two patients of the present series as well as in one of those recorded in 1934. In Case 1 these were described as cramp-like and were severe enough to keep the patient awake at night. In Case 4 they were the first symptom, resembling at their onset the pains of malaria. Although at first transient, the pain returned as radiating pains in the lumbar region, thighs, and legs down to the feet. In Greenfield's Case 2 (1934), the first symptom was shooting pains in the legs, severe enough to cause sweating. It was tempting to relate this symptom to the degeneration of the dorsal roots, which was present in Greenfield's Case 2, but no degeneration of these was found in Case 1 of the present series. This symptom, however, as well as the degeneration of the dorsal columns when it occurs, links these cases with those of polyneuritis associated with carcinoma described by Denny-Brown (1948) and by Lennox and Prichard (1950).

Mental deterioration was also a fairly early symptom in three of these cases, as also in Greenfield's (1934) cases. In Case 2 it took the form of loss of memory for recent events with relative preservation of memory for those long past. In this respect the subacute cases of cortical cerebellar atrophy differ from the more chronic cases in which the mind usually remains clear.

The cerebrospinal fluid showed excess of cells and protein in the three cases associated with carcinoma. In one of these a strong Lange reaction of paretic type was also present. Similar fluids with excess of cells and protein were recorded by Greenfield (1934) and Munch-Petersen (1947), and fluids with abnormal Lange reactions but no excess of cells by Parker and Kernohan (1933), Kennard (1935), and Brouwer and Schlesinger (1947).

Pathology.—The most striking fact that appears in surveying these subacute cases of cortical cerebellar degeneration is that 11 of the 16 have had carcinoma. Not all have died of this, and it is often impossible from the details given to estimate to what extent carcinoma was responsible for death. In two of the three cases of bronchial carcinoma (Greenfield, 1934, and Case 3 of the present series) death was certainly hastened by carcinoma, but in Case 4 the immediate cause of death was cerebellar haemorrhage following a subtentorial craniotomy. In five cases there was carcinoma of the ovary (Parker and Kernohan, 1933; Kennard, 1935; Zülch, 1936; Brouwer and Schlesinger, 1947; and Case 1 of the present series). In two cases, Zülch (1936) and Alessi (1940), there was uterine cancer. Casper's case had a recurrence of mammary carcinoma, and in Greenfield's Case 1 (1934) a tumour of the breast had been removed within a year of death, but as the post-mortem examination was limited to the brain and spinal cord it was not known whether the tumour had recurred.

The relationship of carcinoma to the disease of the nervous system is not very clear. That it has some such relationship is evident from the much higher incidence of carcinoma in these cases with a subacute course (11 or 12 out of 16 cases) than in those with a more gradual onset and slower course. Thus Parker and Kernohan only cite one case of carcinoma of the pancreas (Lhermitte, 1922), among 10 cases of chronic parenchymatous cortical cerebellar atrophy. The curious case, with a rapid onset and then a prolonged standstill of symptoms, reported by Bertrand and Godet-Guillain (1942a) appears to be the only case associated with carcinoma among the many cases of chronic cortical cerebellar atrophy reported since Parker and Kernohan's paper and does not therefore affect their figures. Considering the average duration of symptoms ($17\frac{1}{2}$ years) in these 11 chronic cases and the fact that seven of them reached their sixtieth year, the incidence of carcinoma cannot be shown to be greater in them than in the general population. It is also remarkable that in the 11 subacute cases with definite carcinoma, the primary site of tumour has been most often in the lung and ovary.

Cerebellar Degeneration.—In subacute cortical cerebellar degeneration there is usually a wide-

spread degeneration and disappearance of Purkinje cells, with a lesser degree of degeneration of the neurons of the granular layer and little or no damage to the basket cells and tangential fibres. This degeneration is diffuse affecting the vermis at least as much as the hemispheres. In two of the four cases here reported the degeneration of Purkinje cells was almost complete ; very few remained and these were severely degenerated. In the two other cases the degeneration was earlier and much less universal. In Case 2 it was most evident in the vermis where there was considerable evidence of myelin katabolism ; a larger number of torpedoes were also present on the axons of the Purkinje cells. In addition to slight loss of Purkinje cells and granule cells there was in this case considerable loss of basket cells and fibres. This is unusual in cortical cerebellar atrophy, especially in subacute cases in which this system is usually relatively if not completely spared. In Case 4 the loss of Purkinje cells was greater, and was associated with the microglial " bush-work " which is often seen in the more acute focal degenerations of Purkinje cells, but is unusual in diffuse cerebellar degenerations. Here also some loss of granule cells was seen but the basket cells appeared to be intact.

The nucleus dentatus showed only minor changes in these four cases and there was no evidence of degeneration in the superior cerebellar peduncle. This system has, however, shown a varying degree of degeneration in four of the 16 cases under review (Greenfield's Case 2, 1934; Kennard, 1935; Brouwer and Schlesinger, 1947 ; Munch-Petersen, 1948).

Degeneration of the long tracts of the spinal cord was present in the three cases of the present series associated with carcinoma, as also in Casper's (1929) case, Greenfield's (1934) cases, and one of Zülch's (1936) cases. In several others either no examination was made of the spinal cord or it was only stained by the Weigert-Pal technique, which might well have failed to demonstrate early degeneration. In our cases degeneration was most common and usually most advanced in the direct spino-cerebellar tract. Next in frequency came degeneration of the dorsal columns. Degeneration of dorsal roots was not found except in Greenfield's Case 1 (1934). The pyramidal degeneration was rarely evident at the level of the medulla and was most severe in the lumbar segments of the cord. In the dorsal columns also the degeneration appeared to be oldest in the parts of the nerve fibres which are furthest from the corresponding nerve cells in the dorsal root ganglia, but Zülch draws attention to the special incidence of the degeneration on Flechsig's middle root zone, which is primarily affected also in tabes dorsalis.

The presence of spinal degeneration in at least seven of the 16 cases of subacute cortical cerebellar degneration under review make it more than a casual accompaniment, and justify the name " subacute spino-cerebellar degeneration " used by Greenfield (1934). At the same time, the complete integrity of the spinal cord in Case 2 of the present series, and the absence of degeneration in one or another of the long tracts in other cases where methods to demonstrate recent degeneration have been employed, indicate that spinal degeneration is not constant. It may be more common in the cases associated with carcinoma, but the number of cases adequately examined is too small for any certain knowledge on this point. This assumption, however, would bring the spinal degeneration into line with the peripheral neuropathies found in association with carcinoma (Denny-Brown, 1948), an association which Lennox and Prichard (1950) have shown to be more than a chance one.

The meningeal and perivascular lymphocytic infiltrations which were found in the three cases of this series associated with carcinoma deserve a brief mention. Such infiltration was found also in the neighbourhood of degenerated systems in the two cases described by Greenfield (1934), but, apart from these five cases, has only been found in one other, that of Brouwer and Schlesinger (1947). In spite of the pleocytosis in the cerebrospinal fluid in his case, Munch-Petersen (1947) found no such infiltration. We consider it a reaction to rapidly degenerating nervous tissue (" symptomatic " in Spielmeyer's sense) rather than as having any aetiological significance.

In this series of cases the inferior olives were normal or almost so, the gliosis and slight loss of neurons in Case 3 (Fig. 9) being the only definite change. The inferior olives were also stated to be normal in 11 of the 12 other cases in the group under review ; the only exception was the case of Schroeder and Kirschbaum (1928) in which considerable damage to this nucleus was seen, many neurons being lost and others reduced to shadows. In this respect the group of cortical cerebellar degeneration differs from that of hereditary cerebello-olivary degeneration. It seems probable that the olivary degeneration in these cases is secondary to degeneration in the cerebellar cortex as first suggested by Holmes (1907) seeing that it is limited to the parts of the olive which correspond to the most degenerate areas of cerebellar cortex (e.g., dorsal laminae of the olives when the superior cerebellar convolutions are most degenerated) ; but if so it is not clear why it should be more often present in familial than in non-familial cases of the same chronicity. It is probable, though not certain, that

the olivo-cerebellar fibres terminate as mossy fibres among the neurons of the granular layer. If so, trans-synaptic degeneration of the olivary neurons should follow degeneration of the granule cells, and is not so likely to occur when the Purkinje cells are more selectively damaged. On the other hand the subacute familial cases of cerebello-olivary degeneration reported by Akelaitis (1938) suggest that the combination of olivary with cerebellar cortical degeneration may be inherent in the hereditary gene.

Aetiology and Pathogenesis.—In seeking for an explanation of the rapid degeneration of Purkinje cells in the group of cases under review, we must take into account the special vulnerability of these cells which has been shown both in human disease and in experimental studies. There are, in fact, many extrinsic poisons and abnormal metabolic states to which the Purkinje cells are particularly vulnerable. These include ischaemia, e.g., from temporary arrest of the circulation (Kabat, Dennis, and Baker, 1941), heat stroke (Freeman and Dutnoff, 1944 ; Krainer, 1949), the toxins of typhus fever and scarlatina (Spielmeyer 1922), and various poisons including lead (de Villaverde, 1927). The effect of alcohol on cerebellar functions is well known, and chronic intoxication has been blamed as the cause of cerebellar degeneration in several cases, but in many of these the symptoms have continued to progress in spite of total abstinence from alcoholic drink, and in other respects the relationship as to cause and effect is by no means clear. Zülch (1948) has collected 27 cases of cortical cerebellar degeneration which he could attribute to a toxic cause. These cases ran an " acute or subchronic " course. The suspected cause was neoplasm in eight, alcohol in five, enteritis in four, syphilis in four, tuberculosis in two, and other toxic factors in four.

FIG. 11.—Cerebellar cortex of a rabbit which had received an intracerebral injection of material from the lymph node of a patient with lymphadenoma. Note the complete disappearance of Purkinje cells without other change. × 150. (By the courtesy of Dr. Ruby O. Stern).

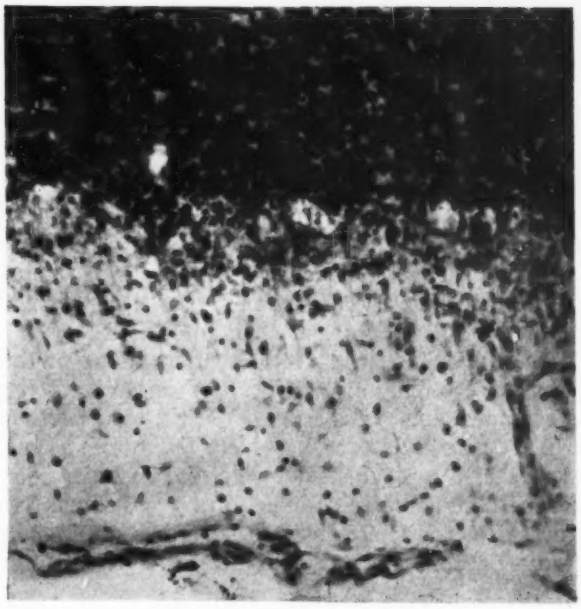

FIG. 12.—Cerebellar cortex of a guinea-pig which had received an intracerebral injection of primate bone marrow. There is in this area disappearance of Purkinje cells associated with a mobilization of the microglia. × 150 (Nissl stain). (By the courtesy of Dr. Lester King.)

The association of cancer with rapid degeneration of Purkinje cells recalls the experimental work of Gordon (1932) on lymphadenoma, and the subsequent experiments of Friedemann and Elkeles (1933) and of Kelser and King (1936), who showed that intra-cerebral injections of primate bone marrow produced in rabbits and guinea-pigs wholesale destruction of Purkinje cells. This effect was later traced by Edward (1938) and by Turner, Jackson, and Parker (1938) to the action of eosinophil leucocytes. It is well known that a high eosinophilia may appear in the blood in cases of carcinoma, especially of the ovary, but there is no record of such an association in any of the reported cases of subacute cerebellar degeneration, nor is it known whether, or to what extent, there was carcinomatous invasion of the bone marrow in these cases.

Parker and Kernohan (1933) suggested that chronic infection by a virus might play some part in the aetiology of the disease. While there is more evidence at the present time than in 1933 that subacute or even chronic disease of the nervous system may be caused by viruses, the systematized nature of the disease does not favour such an aetiology. Although in some cases perivascular and meningeal infiltrations have been present, we regard these, as has been said, as secondary to the rapid degeneration of neurons, and as having the same significance as the mobilization of microglia into " bush-work " in the cerebellar cortex. The special attack of the virus of " louping-ill " on the Purkinje cells in the sheep and monkey instanced by Parker and Kernohan does not appear to occur in man, as no symptoms suggesting cerebellar disease have been seen in human cases of infection by this virus, nor does the closely related virus of Russian tick-borne encephalitis tend to affect the cerebellum selectively.

Bertrand and Godet-Guillain (1942b) found a peculiar degeneration of the granule cells in 14 of 16 cases dying of carcinoma. They describe the granule cell layer as having an iced (" glacé ") naked-eye appearance, and its nuclei, microscopically, as staining poorly by Nissl's method, many having indefinite contours. The Purkinje cells in these cases appeared normal. An examination of 21 cases dying of carcinoma at the National Hospital, London, during recent years has not confirmed these findings. In only one was this change in the granule cells seen ; it was of moderate degree and was confined to the deeper lamellae, the more superficial, both on the upper and lower surfaces, being intact. The patient died early in August and the post-mortem examination was not made till the following day, when autolytic changes were present in the organs of the body cavity ; for example, the nuclei of the convoluted tubules of the kidney completely failed to stain. It is true that the majority of these patients died from spread of the carcinoma to the brain or spinal cord, rather than from its effects on the metabolism of the body. We agree with Bertrand and Godet-Guillain that this change in the granule cells is frequently seen in patients dying in diabetic coma. The change in the granular layer does not appear to have any clinical counterpart, and the early and partial character of the nuclear degeneration, added to the fact that it is sometimes confined to areas of cortex which lie at some depth from the surface, suggest that the condition is partly agonal and partly due to post-mortem autolysis, that is, changes in the cells beginning shortly before death may render them especially liable to autolytic changes.

The granule cell layer is generally much less vulnerable than the layer of Purkinje cells, the only other known cause of selective degeneration of the layer being poisoning with methyl mercury salts (Hunter, Bomford, and Russell, 1940).

The nucleus dentatus is also prone to be affected by severe toxic states such as typhus fever (Spielmeyer, 1921) and may show degenerative changes due to the fatal illness (Scherer, 1932). It is therefore wise to discount the part played by degenerative changes in this nucleus in causing symptoms unless well established myelin degeneration is found in the superior peduncle.

Conclusion.—It is clear that we are not dealing here with a sharply defined pathological syndrome or disease entity but with rare cases in which degeneration of Purkinje cells comes on rapidly, sometimes associated with degeneration of related systems and tracts, especially the spino-cerebellar tract and the superior cerebellar peduncle. In the majority of these subacute cases carcinoma appears to play an aetiological part, either by some special alteration of the bodily metabolism or in combination with some other factor at present unknown. There is no evidence that heredity plays any part in the aetiology, but the processes of local ageing, called by Gowers " abiotrophy," and the special vulnerability of the Purkinje cells and nucleus dentatus probably determine the site of attack. That the equally vulnerable cells of the cerebral cortex may also be affected is shown by the association of dementia in many of the cases, but technical difficulties, especially the large area of cortex to be examined, make a histological assessment of the degree of degeneration in it difficult and uncertain.

Summary

Four cases of subacute cortical cerebellar degeneration are described. In three of these there was also degeneration of the long tracts of the spinal cord (direct spino-cerebellar in all, pyramidal in one, and dorsal columns in the other two).

In these three cases there was also carcinoma, of the bronchi in two and of the ovary in one.

Progressive dementia appeared soon after the onset of cerebellar symptoms in three of the four cases. Diplopia of the cerebellar type was present in all and was an early symptom in three. Cramp-like pains in the legs heralded the onset of cerebellar symptoms in two cases.

A review of the literature shows a high correlation of carcinoma with subacute cortical cerebellar degeneration. Of cases which have run their course in two years, more than two-thirds have had carcinoma, although this has not always been

clinically evident. The more chronic forms of cerebellar degeneration show no such correlation.

In considering the pathogenesis of the disease, emphasis is laid on the special vulnerability of the Purkinje cells to extrinsic poisons or intrinsic metabolic disturbances, but no explanation is found in this for the rarity of the disease.

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ISCHAEMIC LESIONS OF PERIPHERAL NERVES: A REVIEW

BY

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For more than 50 years French and German authors have written about ischaemia as a cause of peripheral neuritis. Joffroy and Achard (1889) and Dutil and Lamy (1893) were among the first to describe ischaemic neuritis occurring in cases of peripheral vascular disease. Lapinsky (1899) drew attention to nerve lesions which were the result of acute arterial occlusions. In a lengthy article he discusses in great detail the sensory disturbances and paralyses which follow arterial thrombosis and embolism, and attributes them to lesions of ischaemic origin of the peripheral nerves Desplats and Baillet (1911) described further cases in which they believed that nerve lesions had developed as a result of ischaemia, but the evidence which they put forward in support of their opinion is far from convincing. Foerster (1912, 1913) wrote extensively on the subject of arteriosclerotic neuritis. More recently Gallavardin, Laroyenne, and Ravault (1925), Coste, Bolgert, and Debray (1933) and Schlesinger (1933) have all reported cases in which there was a clear connexion between the presence of ischaemia and a peripheral neuropathy.

In America "neuritis of vascular origin" has long been recognized as a clinical entity. Under this heading, Woltman (1938) discusses tourniquet paralysis, Volkmann's ischaemic neuritis, neuritis associated with infarction of larger vessels, arteriosclerotic and senile polyneuritis, and neuritis associated with periarteritis nodosa. Fetterman and Spitler (1940) refer to trauma, embolism, arteriosclerosis, thromboangiitis obliterans, syphilis, periarteritis nodosa, and polycythaemia vera as causes of vascular disorders of the peripheral nerves.

Although British authors appear to have been familiar with the concept that vascular disturbances could result in lesions of the peripheral nerves, little was written on the subject until the outbreak of the recent war. Collier (1932), for example, in his Morrison lectures on "Peripheral Neuritis" refers to the possibility that vascular lesions may be responsible for certain types of diabetic neuritis, but makes no other mention of the subject. A similar lack of reference to ischaemic neuropathies is found in other articles on neuritis and in the standard neurological textbooks.

In 1942 Adams reviewed the literature on the blood supply of nerves and included in his review a summary of the clinical evidence that lesions of nerves could be due to interference with their blood supply. Since then the papers of Seddon and his colleagues (Holmes, Highet, and Seddon, 1944; Seddon and Holmes, 1945) and Parkes (1945) on traumatic ischaemia of peripheral nerves have stimulated further interest in all aspects of the problem of nerve ischaemia.

The proper approach to any clinical problem is from an understanding of its anatomical and physiological background. Before discussion of the clinical aspects of nerve ischaemia it is therefore important to consider what is known of the blood supply to nerves, and what has been observed by physiologists and others in experiments on both animals and man in which the circulation to peripheral nerves has been disturbed.

Anatomy and Physiology

Blood Supply of Nerve.—Recent authoritative reviews of this subject have been published by Adams (1942) and Sunderland (1945).

All nerves receive a good blood supply through their vasa nervorum. As the main nerves of a limb pass distally they are supplied with nutrient arteries by adjacent vessels. The majority of nutrient arteries are either direct branches of the main arteries of the limb or subsidiary branches of arteries which, on their way to supply muscles, cross or run close to a nerve. The origin and number of the nutrient arteries supplying any given nerve are variable and there are long segments of

nerve which do not receive a nutrient artery. When the artery approaches the nerve it may behave in a number of ways, but usually, either before or after it enters the epineurium, it divides into two branches each of which, after pursuing a tortuous course, either proximally or distally, anastomoses with similar branches from adjacent nutrient arteries. Thus a continuous anastomosis is formed within the nerve trunk. When a nerve divides or gives off a branch, an anastomosis continuous with that on the parent trunk accompanies each division or branch. Arteriolar branches from the primary divisions of the nutrient arteries form an interfascicular network from which arises the capillary plexus supplying the nerve tissues.

The blood supply of a nerve is thus fundamentally segmental, but a feature of the arrangement of the intraneural vessels is the considerable overlap of supply between nutrient arteries entering the nerve at different levels. This means that in any given segment of nerve it is improbable that a single vessel will dominate the circulation, and in the event of one of the regional nutrient arteries being occluded, a preformed collateral pathway is at once available.

Effects of Ischaemia upon Nerves.—Three types of experiment illustrating the effects of ischaemia upon nerve must be considered :—

Anatomical Studies.—A number of workers have tried to produce ischaemia of peripheral nerves by interfering with their blood supply. As typical examples of such attempts the recent experiments of Adams (1943) and Roberts (1948) may be cited. In the rabbit, Adams ligated the inferior gluteal artery and all other nutrient arteries supplying the sciatic nerve between the hip and knee, but was unable to find histological evidence of nerve ischaemia except in two cases in which considerable mobilization of the nerve was necessary. Roberts attempted to produce ischaemia of the sciatic nerves of dogs by a variety of procedures. In acute experiments, after he had interfered with the blood supply to one sciatic nerve, he outlined the blood vessels of the nerves by injecting a dye into the aorta. Ligation of a single nutrient artery produced only a relative ischaemia of a short segment of nerve. A length of nerve could be made almost completely bloodless either by stripping its epineurium or by stretching it. Embolism of the nutrient arteries was produced by injecting into them either lycopodium spores or sterile powdered graphite. When this was done, patchy areas of ischaemia were produced throughout the nerve. A segment of nerve constricted by a tourniquet or isolated between two ligatures remained ischaemic when the constriction was removed. In long term survival experiments ligation of several nutrient arteries, or stripping of the epineurium from a long length of nerve caused only slight and transient interference with function. Experimental embolism produced marked neurological and nutritional disturbances in the foot, but some of these changes might have been due to the lodgement of emboli in small peripheral arteries supplying tissues other than the nerve.

Physiological Studies on Animals.—If a nerve is to function properly it requires an adequate supply of oxygen which *in vivo* it receives through the blood supply. Gerard (1930) studied the effects of anoxia upon isolated nerve and showed that mammalian (dog) nerve was more susceptible to the effects of oxygen lack than nerve from lower vertebrates (frogs), thus indicating the greater dependence of the former upon its blood supply. Earlier Koch (1926) had studied the " current of injury " in the sciatic nerve of the rabbit before and after occlusion of the aorta. He found that the onset of ischaemia was associated with an increase in a previously subsiding injury current. In more recent years important experimental studies of the effects of ischaemia on nerve have been made by Bentley and Schlapp (1943) and Porter and Wharton (1949). A small but definite circulation is essential for the conduction of impulses along a nerve. In normal circumstances the blood supply provides an ample margin of safety. If a nerve alone is made completely ischaemic by interruption of its blood supply, it may receive enough oxygen by diffusion from adjacent vascularized tissues to enable it to continue to function for some time. If a limb is rendered completely ischaemic, conduction fails first in the distal segments of the nerves. Thus in one experiment in which the hind limb of a cat was made ischaemic by a tourniquet applied to the root of the limb, the nerve in the leg became inactive in 30 minutes, whereas that in the thigh continued to conduct up to two hours (Bentley and Schlapp, 1943).

The immediate effect of ischaemia upon nerve, however, is not a depression of conduction but an increase in irritability as Koch's (1926) experiments suggest. Porter and Wharton (1949), working with the cat's peroneal nerve, showed that cessation of the circulation was followed, after a latent period which varied from 15 seconds to seven minutes, by an increase in irritability which reached its maximum in about six minutes and was followed by a rapid loss of irritability so that the nerve became inexcitable in from 10 to 26 minutes from the onset of ischaemia.

Physiological Studies on Man—A number of observations have been made upon human limbs in which the blood supply has been temporarily interrupted by the application of a sphygmomanometer cuff inflated to a pressure greater than systolic blood pressure. The results of such experiments are complicated by the fact that two different factors, ischaemia and direct pressure upon nerves, may be operative. While some authorities (e.g. Denny-Brown and Brenner, 1944) believe that pressure upon a nerve exerts its effect mainly by causing a local area of ischaemia, others (e.g. Bentley and Schlapp, 1943) think that a nerve block produced by ischaemia has different characteristics from one caused by pressure. Nevertheless the results of these physiological studies on human limbs can be applied to clinical problems in many of which both ischaemia and pressure are encountered as possible aetiological factors.

Lewis, Pickering, and Rothschild (1931) described a centripetal paralysis of both motor and sensory functions which began in the finger tips about 15 minutes after the onset of ischaemia produced by suprasystolic compression of the arm. They attributed this paralysis to the effect of ischaemia upon the nerves rather than the nerve endings, and brought forward evidence which suggested that nerves in the proximal portions of the limbs were more sensitive to ischaemia. They contrasted the centripetal paralysis due to ischaemia with the loss of function produced by local pressure with a clamp upon the ulnar nerve ; in the latter case anaesthesia developed uniformly over the whole territory supplied by the nerve. Later Lewis and Pochin (1938) showed that ischaemia did not cause the different modalities of sensation to disappear in a definite order. Defects in the sensations of touch, appreciation of passive movement, heat and cold, and fast-conducted pain appeared almost simultaneously, but the time at which each of these sensations finally disappeared varied considerably ; touch was lost early but the other modalities declined slowly and were lost within a short period of one another. The defect in slow-conducted pain developed later but was noted before the other forms of sensation were lost. The final phase of sensory loss due to ischaemia, however, was a period in which slow-conducted pain was the only sensation which could be elicited. They were unable to correlate the elimination of the different sensory functions with the size or conduction velocity of the nerve fibres thought to subserve these functions. Nevertheless their observations clearly prove that the nerve fibres which are most resistant to ischaemia are slow-conducting fibres conveying the delayed, more intense portion of the double pain response (Lewis, 1942).

The views of Lewis and his colleagues that a paralysis induced by ischaemia begins peripherally and spreads centripetally and that nerve trunks are more susceptible to the effects of ischaemia in their proximal segments, were accepted and apparently confirmed in similar studies by Zotterman (1933) and Kugelberg (1944). Sinclair (1948), however, has recently repeated Lewis's experiments and has questioned some of his observations and interpretations. He found that the sensory paralysis induced by compression of the arm with a sphygmomanometer cuff inflated to above systolic pressure does not show a regular centripetal spread, but that the territories supplied by the major nerves are successively involved, usually in the sequence median, ulnar, medial, and lateral cutaneous of the forearm. He has further suggested that the differences noted by Lewis and his colleagues between the effects of compression of the arm and the forearm and interpreted by them as indicating that nerve fibres become more sensitive to ischaemia as they are traced back from their endings towards the central nervous system, are due rather to anatomical differences between the contours of the arm and forearm and the ease with which the nerve trunks themselves can be compressed in these segments. When the cuff is applied to the arm, complete ischaemia of the hand and forearm is produced, and the main nerve trunks, poorly protected by muscle, are easily compressed against the humerus, whereas compression of the forearm seldom causes complete ischaemia of the hand and the main nerve trunks are well protected from pressure by muscles.

The experiments of Bourguignon and Laugier (1923), Thompson and Kimball (1936) and Kugelberg (1944, 1946) are of a rather different nature. These workers studied the electrical excitability of nerves in the limbs of man during a period of ischaemia produced by the method discussed above. Their results, which are similar to those obtained by Porter and Wharton (1949) on the cat's nerve (see above), may be summarized by saying that a period of increased excitability of the nerves is followed by a decreasing response to electrical stimuli until they become inexcitable approximately 30 minutes after the onset of ischaemia.

The neurological disturbances which occur when the blood supply is restored to an ischaemic limb are also pertinent to a clinical study of nerve ischaemia. When the circulation returns after an occlusion lasting approximately 30 minutes, muscle power and sensation, as judged by clinical

examination, are approximately normal in less than one minute. Barlow and Pochin (1948), however, have shown that complete recovery of the nerves takes considerably longer. By studying the susceptibility of the nerves to a further period of ischaemia, they have shown that after an occlusion of 25 minutes, at least six hours elapse before the nerves return to complete normality. Within a matter of seconds after the return of blood, intense paraesthesiae are felt in the extremity and fasciculation of muscles may be observed. During the last 20 years these phenomena have been extensively studied, and the relevant literature is well reviewed in recent papers by Weddell and Sinclair (1947) and Merrington and Nathan (1949). Different qualities of post-ischaemic paraesthesiae can be distinguished: thermal paraesthesiae, pricking, tingling, and pseudo-cramp. The last refers to a sensation of tension on the muscles and is felt only after long periods of ischaemia. There is a lack of unanimity regarding the site of origin of these paresthesiae and the nerve fibres concerned in their conduction to the central nervous system. Weddell and Sinclair (1947) suggest that they are produced by stimulation of nerve endings during the removal of a chemical substance which accumulates during the period of ischaemia and that they are conveyed by pain fibres. Merrington and Nathan (1949), on the other hand, are of the opinion that the sensations arise in the nerves recovering from the effects of ischaemia and that the fibres concerned are those responsible for the sensations of touch, pressure, and movement. I consider that the latter hypothesis is the more probable, and it is strongly supported by some of Kugelberg's (1944, 1946) observations. He has demonstrated that nerve fibres recovering from ischaemia and particularly those directly beneath the cuff are hyper-excitable; bursts of spontaneous repetitive discharges can be recorded and any stimulus applied to the nerve instead of provoking a single response initiates a burst of impulses. Post-ischaemic paraesthesiae are the clinical manifestation of this abnormal activity in sensory nerve fibres. Similarly fasciculation can be attributed to spontaneous impulses arising in motor nerve fibres, and may also be favoured by an increased irritability of the muscles themselves due to a lowered concentration of ionized calcium as suggested by Reid (1931).

Clinical Observations

Arterial Embolism.—Ischaemia is seen in its purest form as a result of arterial embolism. Since the obstruction to the circulation is sudden and intravascular, the influence of such factors as pressure, haemorrhage, and pre-existing disease in the limb can usually be confidently excluded. As Lewis (1936b) has pointed out, the moment of lodgement of an embolus is seldom, if ever, recognized. The initial symptoms of coldness, numbness, weakness or pain in the limb do not appear until the obstruction to the circulation has been present for some time. Pain in the early stages is due to muscle ischaemia, but numbness, sensory loss, and motor paralysis are the result of ischaemia of the peripheral nerves. If the blood flow is restored within a few hours either by embolectomy or by the establishment of an adequate collateral circulation, the motor and sensory manifestations will rapidly improve and the limb return to normal. On the other hand, if the ischaemia persists for some hours but is relieved in time to prevent loss of the limb from gangrene, persistent motor and sensory disturbances may be observed. Haimovici (1950) found that this was the course of events in 13·5% of 330 cases of peripheral arterial embolism.

In this state of chronic post-embolic ischaemia, lesions of the peripheral nerves are usually accompanied by muscle necrosis and nutritional disturbances of skin and subcutaneous tissue. However, there is reliable evidence that in some cases nerves alone are damaged by the ischaemia (Blackwood, 1944). When patients reach the chronic stage they may continue to complain of pain, but it is seldom severe and is usually of the nature of annoying and rather intense paraesthesiae which tend to subside spontaneously within two to three months. On examination of the affected limb the signs of a peripheral neuropathy may be complicated by the presence of infarcted muscle and contractures of the hand or foot. If the muscles have not been directly damaged by the ischaemia they may be wasted, show coarse fasciculation, and be tender on pressure. A flaccid paresis affecting the most distal muscles may be noted. In the lower limb the ankle jerk is absent. Examination of sensation reveals a distal segmental area of anaesthesia or hypaesthesia associated with a delayed and very unpleasant response to pinprick and pressure stimuli.

In cases in which an embolus has lodged at the aortic bifurcation and has been successfully removed, the residual neurological defect may suggest a spinal root or cord lesion rather than a peripheral neuropathy (Learmonth, 1948, Case 3).

Trauma.—Only recently has ischaemia been recognized as an important factor in the pathogenesis of some nerve lesions which follow gunshot wounds and other injuries of the limbs. In some

cases an association between injury and ischaemia may be obvious ; for example, it may be known that the main artery of the limb has been damaged, but in many cases the possibility that ischaemia is wholly or partly responsible for the nerve lesions may be overlooked unless the limb is carefully examined for evidence of a vascular lesion.

When the main artery of a limb is interrupted, the results are extremely variable. If an adequate collateral circulation is immediately available, the effects may be so minimal that it is difficult to detect any neurological disturbance. On the other hand, massive gangrene of the limb may develop. Between these two extremes there is a group of cases in which the nerves, muscles, skin, and subcutaneous tissues suffer severely from the effects of ischaemia, but the limb as a whole survives. The end-result in these cases is an ischaemic paralysis of the limb. In such cases the nerve lesions may be due entirely to ischaemia or there may have been concomitant injury to both nerves and blood vessels so that, although the nerves are damaged at the level of injury, the effects of ischaemia must be considered in assessing the clinical findings and the prospects of recovery.

In time of war cases of this nature are not uncommon, and an excellent description of the syndrome of ischaemic paralysis was given by Tinel (1917). During the recent war considerable attention was focused on such cases, and elsewhere I have reviewed the recent literature and given details of other cases observed at three of the British peripheral nerve injury centres (Richards, in M.R.C. Report in preparation).

If it is known that a main artery has been injured and there is clinical evidence of ischaemia (infarcted muscle, gangrene of digits), it is not difficult to surmise that the nerve lesion may also be due to ischaemia, but the problem is not always so simple. For many years it had been recognized that the complication of fractures in the region of the elbow known as Volkmann's contracture was commonly accompanied by serious peripheral nerve lesions which, despite encouraging findings when the nerves were explored at the level of the fracture, seldom recovered well. An explanation for these apparently anomalous findings has only recently been provided by the work of Griffiths (1940) and Seddon and his colleagues (Holmes and others, 1944). The former showed that the majority of cases of Volkmann's contracture, if not all, are due to an arterial injury complicating the fracture, and that the contracture is the result of ischaemic necrosis of the flexor muscles in the forearm. Holmes, and others (1944) made a detailed study of the nerve lesions in seven cases of Volkmann's contracture. They found, as had others before them, that in the majority of cases the nerves were normal at the site of the fracture. When the nerves were dissected distally, a remarkable change was found where they entered that portion of the limb in which the muscles were necrotic ; they appeared shrunken and avascular and resembled strands of fibrous tissue rather than nerves. The inference from these findings was that the nerves, like the muscles, had been damaged by ischaemia, and the authors concluded that this was the aetiology of the majority of nerve lesions in cases of Volkmann's contracture. They also described histological changes in the nerves which they regarded as pathognomonic of severe nerve ischaemia ; a great increase in endoneurial collagen sometimes progressing to complete replacement of the nerve bundles by collagen.

A less severe degree of nerve ischaemia than that encountered in cases of classical Volkmann's contracture may be seen in association with fractures which are complicated by considerable swelling of the limb and pressure beneath the deep fascia which temporarily interrupts the peripheral circulation (Parkes, 1945).

Unfortunately there is no typical clinical picture which will enable a diagnosis of traumatic ischaemia of peripheral nerves to be made with certainty. If the main vessel of the limb has been injured either directly by a gunshot wound, or indirectly in association with a fracture, the nerve lesions may be single or multiple. There is a certain amount of evidence to suggest that the larger nerve trunks are more susceptible to ischaemia ; I have seen two cases in which the median nerve only was affected by a high lesion of the brachial artery. If more than one nerve is affected, it is usual for the distal branches to be affected most severely so that the area of sensory disturbance has a segmental (" glove ", " sock ", " carpet-slipper ") pattern and does not correspond to the anatomical territory of one or more nerves. In cases where the nerve ischaemia is the result of pressure beneath the deep fascia, this segmental distribution is confused by the fact that nerves which lie outside the deep fascia, e.g., the saphenous nerve, escape damage.

The quality of the sensory disturbance may be of help in establishing a diagnosis. In some cases of suspected nerve ischaemia the only sensory response which is preserved is a delayed and very unpleasant response to deep pinprick or pressure and best elicited by " pinching " the fingers or toes. The studies of Lewis and Pochin (1938) showed that in experimental pressure ischaemia of a human limb a slow-conducted pain response of this type can be elicited after all other modalities

of sensation have been lost. Wortis, Stein, and Jolliffe (1942) and Parkes (1945) have drawn attention to the important significance which such a finding may have in a case in which a clinical diagnosis of nerve ischaemia is being considered. However, a slow-conducted pain response can be elicited as the only sensory response in a number of other clinical conditions, e.g., tabes dorsalis, peripheral neuritis, and incomplete or recovering nerve lesions due to any cause. The presence of this type of response indicates that the tissues from which it is elicited are supplied only by a few isolated pain fibres (Weddell, Sinclair, and Feindel 1948). Therefore, while a slow-conducted pain response is often a very striking feature in cases of nerve ischaemia, it cannot be regarded as a pathognomonic sign, nor does its absence in association with either complete or incomplete anaesthesia or analgesia exclude a diagnosis of nerve ischaemia.

Assessment of the degree of motor paralysis may be difficult ; often it is hard to tell which muscles are paralysed because they are ischaemic and which are denervated. Thus before a clinical diagnosis of traumatic ischaemia of a peripheral nerve can be made, it is necessary that there should be evidence —absent or diminished pulsation in the peripheral arteries, ischaemic muscles, or areas of superficial gangrene—to indicate that the circulation of the limb is or has been inadequate.

In some cases in which, after careful clinical examination of the limb, the possibility that ischaemia is an aetiological factor has been confidently dismissed, histological examination of excised portions of nerve has revealed evidence of ischaemic damage. Seddon and Holmes (1945) have described a case in which the characteristic histological changes of nerve ischaemia were found only in the distal stump of a divided median nerve. The case was one in which the radial artery had been injured as well as the median nerve, and the authors put forward the following explanation for the ischaemia of the nerve. Division of the nerve had interrupted the longitudinal blood supply from above. This in itself would not be sufficient to cause serious ischaemia of the nerve, but the radial artery had also been interrupted and the median nerve in the lower forearm receives its blood supply from branches of this vessel so that the distal segment of the divided nerve was deprived of its entire blood supply. More recently Woodhall and Davis (1950) have reported that, on routine histological examination of the proximal and distal stumps of nerves removed at operations for nerve suture, they have found changes in the arteriae nervorum and varying degrees of ischaemic damage of the nerve bundles to be not uncommon. Unfortunately they do not state in every case whether the specimens were obtained from patients who had sustained a concomitant vascular injury. They describe one case of thrombosis of the arteria comes nervi ischiadici and one of thrombosis of the artery accompanying the median nerve. In both cases the distal stumps showed an increase in the amount of endoneurial collagen. They emphasize that changes in the arteries and evidence of nerve ischaemia are always more pronounced in the distal segments, and therefore suggest that the interruption of the longitudinal blood supply of a nerve may not be as harmless an event as has been heretofore believed. They further advise that when the distal segment of a divided nerve has to be freed for some distance to enable suture to be performed, it is important to preserve carefully all vessels running to the nerve.

Despite these discouraging pathological findings, it has been my experience that injured nerves may regenerate well in an ischaemic limb. In one case of severe ischaemia of the upper limb the ulnar nerve, sutured in the axilla, regenerated sufficiently well to reinnervate the abductor minimi digiti muscle which had previously been found by biopsy to contain areas of infarction. The poor functional results in cases of ischaemic paralysis are due not so much to failure of nerve regeneration as to the effects of the ischaemia upon the muscles, joints, skin and subcutaneous tissue.

These observations suggest that the importance of ischaemia in the aetiology and prognosis of many cases of peripheral nerve injury has previously been much under-estimated.

Tourniquet Paralysis.—Fortunately it is a rare event for the use of a tourniquet to be followed by persistent paralysis of the limb. When tourniquet paralyses do occur, they are seldom reported, but Eckhoff (1931) and Speigel and Lewin (1945) have reviewed the available literature and described several cases. Elsewhere I have discussed the condition and reported two further cases (Richards, M.R.C. Report). Tourniquet paralysis occurs most often in the upper limb, and the radial nerve is always affected, in some cases alone, in others along with the median and ulnar nerves. Only three cases of the condition in the lower limb have been recorded. As a rule the nerve lesions are not serious and recover spontaneously in from three to six months, but there is evidence that sometimes the paralysis may be permanent. In the mildest cases the paralysis is purely motor and is the result of a non-degenerative lesion of the nerves—a neurapraxia (Seddon, 1943)—but all grades from this

to complete motor and sensory paralysis without recovery have been recorded.

It is apparent that there are two possible aetiological factors which, acting either alone or together, may produce the nerve lesions—ischaemia and pressure. An efficient tourniquet causes complete ischaemia of the limb distal to the site of application. Earlier in this paper the results of experiments in which the arm was compressed by a sphygmomanometer cuff were discussed. It was shown that ischaemia of a limb produced in this way results in a peripheral type of paralysis affecting both motor and sensory functions. On release of the pressure rapid recovery occurs and is accompanied by post-ischaemic paraesthesiae and fasciculation in the muscles. It is tempting to assume that if the circulation were cut off for a sufficiently long period, pathological changes would occur in the nerves and give rise to a persistent paralysis. There are reasons why this simple explanation for the occasional occurrence of tourniquet paralysis should be questioned.

First, in cases in which paralysis has followed, the length of time for which the tourniquet has been applied is often no longer than that in similar cases in which no untoward effects have been observed, and in some cases has been no longer than that (30–40 minutes) which is often employed in experiments on man. I have seen a case in which a very tight band on the arm for only 20 minutes caused paralysis of the median, ulnar, and radial nerves which, three weeks after the incident, was still clinically complete. Perhaps this is an exceptional instance, but all authors agree that tourniquet paralysis occurs after both short and long operations. This is in keeping with the experimental observations of Denny-Brown and Brenner (1944); in the cat they found that " the amount and duration of pressure (with a tourniquet) necessary to cause persisting paralysis are extremely variable". It seems probable that individuals may vary considerably in regard to the susceptibility of their nerves to pressure, and that a degree and duration of compression which is harmless in one patient in another may produce either a transient or persistent paralysis. Even if one allows that there is a natural tendency to underestimate the time for which a tourniquet has been applied, especially in cases in which paralysis has followed, it is certain that nerves can recover from a period of pure ischaemia greater than the longest time for which a tourniquet is ever applied. Lewis (1936a), for example, states that nerves recover after being ischaemic for 12 or even 20 hours.

Secondly, the type of paralysis is not always similar to that observed in experiments on compression paralysis. A peripheral segmental paralysis is the exception rather than the rule, and the radial nerve is always that most seriously affected in cases of tourniquet paralysis, whereas Sinclair (1948) found that the median nerve was the most susceptible to compression paralysis. In two of the cases recorded by Speigel and Lewin (1945) irreparable damage was done to the radial nerve, yet the other nerves escaped completely.

There are several pieces of evidence which incriminate direct pressure upon the nerves as an important factor. In mid-arm, where a tourniquet is usually applied, the radial nerve is more easily compressed against the humerus than the other main nerves. The relative infrequency of tourniquet paralysis in the lower limb may be explained by the fact that the sciatic nerve in the thigh is well protected by muscles. Although details of the type of tourniquet used are not available in all the reported cases, in many either a narrow rubber tube or an elastic bandage, both of which can be applied to a limb with considerable force, were used and often applied directly to the limb. A case of tourniquet paralysis following the use of a sphygmomanometer cuff has yet to be reported. There is no difference between a mild case of tourniquet paralysis and a pressure palsy of the radial nerve due to sleeping on the arm (" Saturday night palsy ").

In summary, there is insufficient evidence for tourniquet paralysis to be regarded as a pure ischaemic neuropathy. It is probable that ischaemia is an aetiological factor, especially in cases which follow prolonged occlusion, but the injurious effects of direct pressure upon the segment of nerve beneath the tourniquet appear to be more important.

Occlusive Vascular Disease.—" Ischaemic neuritis " is recognized to be the cause of a type of rest pain in patients suffering from occlusive vascular disease (Slessor and Learmonth, 1949).

The importance of nerve lesions in such cases was recognized first by Joffroy and Achard (1889). They reported the case of a woman aged 63 who had occlusive vascular disease of the lower limbs with a marked degree of atrophy of the muscles of the legs and severe pain. At necropsy they found an extensive obliterating arteritis of the vasa nervorum and a patchy Wallerian degeneration of the nerve fibres. Four years later Dutil and Lamy (1893) described a similar condition in a man aged 40. This case is of interest as the pathological findings are given in great detail and are typical of those found by Buerger (1908) in the group of cases to which he gave the name thromboangiitis obliterans. Subsequently there have been several clinical and pathological studies on the state of the

nerves in cases of thromboangiitis obliterans (Meleney and Miller, 1925 ; Barker, 1938), arteriosclerosis obliterans (Gallavardin and others, 1925 ; Priestley, 1932), and " spontaneous gangrene " (Panchenko, 1938).

Although mild degrees of neuropathy are probably present in the majority of cases of occlusive vascular disease, severe neuropathy is not common ; Schlesinger (1933) reported an incidence of 4·7% in 470 patients of all ages suffering from intermittent claudication, and Goldsmith and Brown (1935) found it in only 7% of cases of thromboangiitis obliterans. It occurs in the lower limbs only and has certain very characteristic features.

" Ischaemic neuritis " is seldom encountered where there is a short history of vascular disease. The patient is nearly always a man who has a long history of claudication or other symptoms indicating a moderate degree of peripheral ischaemia followed by an episode which suggests occlusion of a major proximal vessel. Perhaps because the muscles and skin have already become adjusted to a relatively poor blood supply, the limb survives a major vascular catastrophe which, had it occurred in a previously normal limb, in all probability would have resulted in gangrene. The nerve trunks cannot accommodate themselves to a blood supply less than their basic needs and consequently the patient finds himself left with a useful but painful limb. Thus the presence of ischaemic neuritis indicates a severe degree of peripheral ischaemia. Although a patient who suffers from " ischaemic neuritis " nearly always has occlusive vascular disease of both lower limbs, the " neuritic " symptoms are frequently unilateral and indicate the limb most severely affected.

Pain is always the predominant symptom and is often severe and continuous. Superficial and deep-seated pains can be distinguished. The former is described as burning ; " red-hot ", " on fire ", " hyperaesthesia ", " like a dentist's drill under the skin " are expressions used by patients to describe their sensations. The pain is felt over large areas of the limb which rarely correspond to the anatomical distribution of a nerve or nerves. The deep pains are more apt to be paroxysmal and resemble the lightning pains of tabes dorsalis ; patients describe bursts of pains which radiate from the base of the toes up the leg to the knee and even into the thigh. According to Goldsmith and Brown (1935) paroxysms of pain of this nature may be accompanied by attacks of discoloration of the foot. These pains are always worse at night, are aggravated by heat but may be relieved by moderate warmth. They are frequently eased when the feet are pendent and supported, and for this reason patients with " ischaemic neuritis "* often sleep sitting in a chair with their feet on a low stool. In my experience, morphine is the only analgesic which has a uniformly satisfactory effect in relieving the pain. Codeine, pethedine, physeptone, and other analgesics may all give temporary relief, but soon lose their effect, and, as pain usually persists for months, surgical measures for its relief are frequently necessary. As the condition is encountered only in the lower limbs, cordotomy can be relied upon to give complete relief and often gives the patient a useful, pain-free limb.

In addition to these typical pains, patients may complain that their foot feels numb, is unduly sensitive to cold, and that the skin of the sole feels unduly thick or " cushioned ".

Apart from gross muscle wasting, objective neurological disturbances are minimal ; absent or diminished ankle jerks, patches of hypaesthesia and hypalgesia, and on the sole the characteristic delayed, unpleasant and persisting response to pain and pressure stimuli are the features most commonly observed.

Diabetes Mellitus.—The importance of a vascular factor in the pathogenesis of diabetic neuropathy is a problem which has received considerable attention but cannot be said to be finally settled.

Collier (1932) described four types of diabetic " neuritis " : (1) an interstitial neuritis or fibrositis presenting as sciatica, lumbago, etc. ; (2) the rapid and painless onset of complete and irrecoverable paralysis of one or more large peripheral nerve trunks ; (3) paralyses of oculomotor nerves ; and (4) a general peripheral neuritis. The second type he believed to be due to a thrombosis of the artery supplying the nerve trunk, and he suggested that similar vascular lesions might be one of the factors responsible for the fourth group.

The pathological studies of Woltman and Wilder (1929) on the peripheral nerves of diabetic patients revealed a high incidence of arteriosclerosis in the vasa nervorum.

Jordan (1936) found that 95·8% of 120 cases of diabetes with acute and severe neuropathy presented signs of peripheral vascular disease. While he suggested that the latter might be a causative factor in the production of the neuropathy, he was inclined to regard both conditions as the result of some common factor associated with the diabetes.

Randall (1938) studied the lipid composition of

* Throughout this review the term " ischaemic neuritis " is used to refer only to this painful type of neuropathy which occurs in occlusive vascular disease.

normal nerves and of nerves from cases of arteriosclerosis and diabetes mellitus. In the normal nerves the lipid constituents were the same in both proximal (femoral and sciatic) and distal (posterior tibial) nerves, but the nerves from both the arteriosclerotic and diabetic subjects were found to show a decrease in phospholipids, cholesterol, and cerebroside and an increase in neutral fat, and these chemical changes were more pronounced in the distal nerves. He attributed these changes to "an inadequate blood supply and the concomitant anoxaemia."

Kauvar (1941) reviewed the relation of arteriosclerosis to diabetic neuropathy of the lower extremities and divided his diabetic patients into three groups: (1) young, uncontrolled diabetics with peripheral neuritis but without evidence of vascular disease; (2) uncontrolled diabetics with neuritis and vascular disease; and (3) controlled diabetics with neuritis and generalized arteriosclerosis. The first group consisted of only two patients in whom the neuritis rapidly recovered when the diabetes was controlled. In the other two groups there was a definite correlation between the extent of the vascular disease and the neuropathy. In the discussion he pointed out that diabetic neuropathy seldom occurs in a patient below the age of 40 years, that it shows a marked predilection for the lower limbs, and that it is usually not related to the severity or degree of control of the diabetes. He therefore concluded that arteriosclerosis and the resultant ischaemia are major causes of diabetic neuropathy.

A similar view is expressed by Dry and Hines (1941) who postulate that a common mechanism, namely, involvement of the nutrient vessels, underlies the neuropathy, retinopathy, and intimal arteriosclerosis which occur in diabetes, and conclude that "diabetic neuritis is essentially an ischaemic neuritis and its genesis is dependent on interference with the vascular supply to the nerve bundles".

Rundles (1945), however, in a more extensive review in which the subject of diabetic neuropathy is considered from a more general viewpoint, does not agree that peripheral vascular disease and neuropathy are frequently associated; in 80% of his 125 cases of diabetic neuropathy there was no evidence of peripheral vascular disease. While he agrees that the two conditions may co-exist, he rejects the hypothesis that ischaemia is an important aetiological factor and ascribes the neuropathy to "the abnormal metabolism of chronically unregulated diabetes".

There is no doubt that a peripheral neuropathy can and does occur in diabetic patients who do not have symptoms or signs of peripheral vascular disease. On the other hand, it is common for the elderly arteriosclerotic diabetic to develop a neuropathy which progresses with his vascular disease. This, however, as Treusch (1945) points out, is only one of several types of diabetic neuropathy. Even in cases where the presence of an ischaemic factor appears obvious, it is probably not the only one. Diabetics appear to develop neuropathy with less severe ischaemia than that necessary to cause nerve lesions in non-diabetics with either arteriosclerosis or thromboangiitis obliterans; ischaemic neuritis is seldom, if ever, seen in a woman who is not a diabetic.

Periarteritis Nodosa.—Considerable attention has recently been focused on this disease which is either becoming more common or is being diagnosed more frequently. Among the protean manifestations of periarteritis nodosa, peripheral neuritis is encountered with a frequency which is variously estimated to be between 12 and 52% of cases (Lovshin and Kernohan, 1948). The neuritis presents in one of two forms: either as a "mononeuritis multiplex", that is an involvement of several individual large nerve trunks either simultaneously or at varying intervals, or as a symmetrical peripheral neuritis.

When neuritis occurs it appears early in the course of the disease and often is the presenting complaint. The onset may be sudden or gradual; pain and paraesthesiae either alone or together are the most frequent initial symptoms and objectively muscular weakness is usually more pronounced than sensory changes.

Although clinical evidence of gross ischaemia of the limbs may be absent, histological studies of nerves from cases of periarteritis nodosa show clearly that the neuropathy is due to ischaemia (Kernohan and Woltman, 1938). Occlusion of nutrient arteries leads to focal areas of infarction in the nerves which result in degeneration of the nerve fibres in the more distal portions of the nerves. The alternative hypothesis that the neuropathy is due to the same mechanism, toxic or allergic, which causes the arterial lesions, is not supported by the histological findings.

Miscellaneous Causes.—There are a number of other conditions in which ischaemia may be partly responsible for the development of a peripheral neuropathy. In haemophilia lesions of the peripheral nerves are uncommon, and when they do occur are usually due to the direct pressure of a haematoma; the nerve most frequently affected appears to be the femoral (Aggeler and Lucia, 1944). Occasionally when haemorrhage beneath

the deep fascia occurs in a limb, there may be serious interference with the circulation and ischaemic lesions of the peripheral nerves may result ; this was the sequence of events in the case reported by Lord (1926) and in the two cases observed by Seddon and quoted by Parkes (1945).

Fetterman and Spitler (1940) describe an ischaemic lesion of the sciatic nerve as the result of an accidental injection of bismuth into the inferior gluteal artery which was thought to have produced multiple emboli in the vasa nervorum. They also stress the role of vascular lesions in the pathogenesis of syphilitic neuritis and attribute to vascular changes in the nerves the pains and paraesthesiae which are experienced in the limbs by patients with polycythaemia vera.

Ischaemia is undoubtedly one of the factors responsible for the neuropathy observed in cases of trench foot, immersion foot, and allied syndromes, but the direct effect upon the nerves of the prolonged exposure to low temperature is equally important. Pressure upon nerves must be considered as a possible third factor in view of the gross swelling of affected extremities which occurs during the period of hyperaemia (Ungley, 1949).

In a recent article Bastos (1949) has suggested that in certain irritative nerve lesions, e.g., traumatic ulnar neuritis due to intermittent pressure upon the nerve in the ulnar groove, the nerve lesion may be responsible for initiating vasoconstrictor impulses which would affect the vasa nervorum distal to the site of the original lesion and thus cause a relative ischaemia of the nerve. He claims that in cases of this nature he has hastened recovery by adopting procedures which cause vasodilatation, e.g., sympathectomy.

Discussion

Peripheral nerves receive an abundant blood supply and the intraneural vascular anastomosis ensures that interference with any one source of supply is unlikely to cause serious interruption of the circulation to the nerve. This is confirmed by the difficulty which is encountered when any experimental attempt is made to produce histological evidence of ischaemic damage to nerve. On the other hand, physiological studies show that nerve fibres cease to conduct soon after their blood supply is cut off. From these observations, it may be concluded that nerves can survive with a blood supply which is much less than that which they require to function properly.

In man, when the circulation to a limb is arrested, a peripheral segmental motor and sensory paralysis develops. This can be shown to be due to ischaemia affecting the peripheral nerves. If the circulation is restored within 30 to 40 minutes, rapid and complete recovery occurs and is followed by paraesthesiae and muscle fasciculation due to a temporary hyperexcitability of the previously ischaemic nerves.

It is not difficult to correlate the clinical findings with these anatomical and physiological observations. A sudden arterial occlusion in a previously healthy limb, as typified by arterial embolism, is associated with the onset of motor and sensory paralysis which begins distally and spreads up the limb but will recover rapidly if the circulation is restored within a few hours ; moreover, patients invariably complain of intense paraesthesiae as " life " returns to the limb. On the other hand, if the blood supply to a limb is gradually reduced, evidence of interference with nerve function is seldom observed ; the incidence of ischaemic neuritis in cases of occlusive vascular disease is low.

Pure ischaemia of this nature is apparently much less injurious to nerve than ischaemia produced by, or associated with, compression. Whereas nerves will recover rapidly after at least 12 hours of pure ischaemia, a persistent paralysis has resulted from as short a period as 20 minutes' ischaemia produced by constriction of a limb. It is difficult to account for this difference but two possibilities must be considered. (1) Pressure of itself is injurious to nerve fibres, and if sufficiently severe will produce a pressure necrosis of the nerve ; this is the view of Allen (1938) and Speigel and Lewin (1945). (2) Pressure damages the blood vessels in the constricted segment of nerve so that even when the pressure is relieved the circulation cannot be restored to that portion of nerve ; this is supported by Roberts's experimental observation that a segment of nerve constricted by a tourniquet remained ischaemic after the pressure was released.

It seems to me that clinically it is possible to distinguish two types of " compression paralysis " : (1) that due to constriction by a narrow band, e.g., a narrow rubber tourniquet in which direct pressure is the major factor and in which damage to nerve trunks depends upon the amount of pressure which each nerve receives, and (2) that due to compression over a considerable length of limb, e.g., pressure beneath the deep fascia following a fracture, in which ischaemia is the major factor and to which the nerves are susceptible in proportion to their dependence upon their blood supply so that the largest nerve trunks suffer most severely. Only the latter type is comparable to the experimental paralysis produced by compression of a limb with a sphygmomanometer cuff inflated to above systolic blood pressure.

The relationship between pain and ischaemic changes in the nerves is of interest. Pain is not an invariable accompaniment of acute arterial occlusion and when it occurs its quality and distribution do not suggest that it is neuritic in origin. Lewis (1936b) has clearly shown that the source of this pain is the ischaemic muscles of the limb. The pain is aggravated by activity of the muscles and is associated with acute tenderness of the muscles. The mechanism of production of the pain is assumed to be similar to that causing intermittent claudication—a pain-producing substance accumulating in the ischaemic muscle. The fibres which convey the sensation of pain must be amongst those most resistant to ischaemia for severe pain may be present, or can be produced by pressure, in the calf, in cases in which all modalities of cutaneous sensation are absent as high as the knee.

" In cases in which sudden arterial occlusion does not lead to gangrene, the symptoms due to sudden occlusion may merge imperceptibly into those of ischaemic neuritis, described by Goldsmith and Brown. The pains tend to be paroxysmal and severe and to cover large areas which do not correspond to any definite nerve distribution. They may persist for weeks or months " (McKechnie and Allen, 1936). This has not been my experience. If the limb has been previously healthy and survives the vascular catastrophe, even although there may be evidence of ischaemia of muscles, nerves, skin and subcutaneous tissue, pain is seldom a prominent feature. In a series of 34 patients with ischaemic paralysis following gunshot wounds of the arteries, only six complained of severe pain and the quality of the pain was unlike that of typical ischaemic neuritis (Richards, M.R.C. Report). In established cases of Volkmann's contracture with nerve lesions due to ischaemia pain is also rare (Holmes and others, 1944).

On the other hand, the most prominent feature of the ischaemic neuropathy which may occur in cases of occlusive vascular disease is severe pain, and objective evidence of loss of nerve function may be minimal. Furthermore, in such cases its onset is often related to an acute occlusion of a large proximal vessel in a limb in which mild symptoms of circulatory insufficiency have been present for some time.

The clinical evidence therefore seems to suggest that when a nerve is acutely deprived of its blood supply, even to the extent of causing infarction, pain may not be a prominent feature and seldom outlasts the acute stage, but, if the blood supply of a nerve is reduced either gradually or by a series of episodes none of which is sufficiently severe to cause necrosis of the entire nerve, then the characteristic pains of ischaemic neuritis will appear.

The nature of the lesion in the nerve which is responsible for the pain is uncertain. Anyone who has seen many cases of causalgia and ischaemic neuritis must have been impressed by the similarity of the pain in the two conditions. The chief difference lies in the diffuse spread of the pain in ischaemic neuritis, but this may be explained by the fact that causalgia is essentially a mononeuritis whereas occlusive vascular disease affects all the nerves of the limb, often in a patchy manner, and causes multiple lesions. The mechanism of the artificial synapse has been invoked by Doupe, Cullen, and Chance (1944) to account for the pain of causalgia. Their view, which has met with considerable acceptance, is that as a result of either disease or injury, defective insulation occurs in the nerve trunk and thus impulses which are constantly passing down sympathetic fibres are able to stimulate afferent pain fibres. It seems not inconceivable that the pains of ischaemic neuritis are due to the presence of multiple artificial synapses in more than one nerve, which have been produced by the defective blood supply to the nerve trunks.

The diagnosis of ischaemic neuritis in cases of occlusive vascular disease is not difficult but the diagnosis of the other types of ischaemic neuropathy may be difficult. There is no typical clinical picture which can be relied upon so that, unless histological proof can be obtained, the diagnosis must be inferred from the presence of other signs suggesting a vascular disturbance in the limb. The difficulty is particularly great in cases of periarteritis nodosa which may present as a peripheral neuritis of either the multiple symmetrical or mononeuritic type. Therefore in neuritis of obscure origin, ischaemic neuropathy and periarteritis nodosa, especially, should be considered.

Summary

From the material presented in this review, it is apparent that there is ample physiological and clinical evidence to suggest the hypothesis that lesions of peripheral nerves can be due to vascular disorders. A short period of ischaemia produces a temporary disturbance of nerve function which, when the circulation is restored, recovers rapidly and completely. Severe or prolonged ischaemia causes structural changes in the nerves, and persistent or even permanent lesions result. In clinical practice ischaemic lesions of peripheral nerves are seen in cases of arterial embolism, after injuries to the limbs in which the peripheral circulation is interrupted either as a result of trauma to a main vessel or by pressure beneath the deep fascia

complicating a fracture, in tourniquet paralysis, in occlusive vascular disease, in diabetes mellitus, in periarteritis nodosa and, less commonly, in a few other diseases. In some of these conditions, e.g., arterial embolism or injury, the nerve lesions are due entirely to ischaemia; in others, e.g., tourniquet paralysis and diabetes mellitus, it is probable that other factors also play a part.

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REPETITIVE DISCHARGES IN HUMAN MOTOR NERVE FIBRES DURING THE POST-ISCHAEMIC STATE

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A number of motor and sensory changes follow the release of a human limb from ischaemia. The sensory changes are necessarily subjective but the motor changes lend themselves readily to delimitation by modern recording methods; it is a little surprising, therefore, to find as great a disagreement between observations in the latter field as in the former. Among these phenomena are bursts of repetitive muscle action-potentials, found mainly in the more distal muscles. They occur in the first phase of recovery from ischaemia and may be spontaneous, but are also induced by voluntary contractions of the muscle and by electrical stimulation of its nerve.

It was considered by Kugelberg (1946a) and by Denny-Brown and Foley (1948) that the repetitive action-potentials were initiated in the nerve, and it seemed necessary for large segments to be in the post-ischaemic state for the response to occur. Magladery, McDougal, and Stoll (1950), on the contrary, have little doubt that repetitive firing takes place distally, most probably at the myoneural junction. Whether this is so is of some importance for its own sake, and also because of the light it throws on the parallel sensory disturbances, so far inaccessible to objective analysis. The following work, therefore, describes experiments which have been made to establish the site of origin of spontaneous and induced repetitive discharges.

Method

For experimental convenience, and standardization, the ulnar nerve and first dorsal interosseous muscle of the hand were used in all experiments; the subjects (including the authors) were all healthy young adults, to some small extent selected for the ease with which their repetitive responses were obtained.

Action potentials were picked up from the muscle by coaxial needle electrodes, amplified by a differential amplifier with an adequate range of frequency response, and displayed on one beam of a Cossor double-beam cathode ray oscilloscope. The other beam was fed with a sinusoidal time-scale at 500 or 100 c/s (intervals of 2 or 10 msecs.).

Bipolar stimulation of the ulnar nerve, by electric shocks of 0·5 msec. duration, was applied above the elbow or at the wrist, through surface electrodes with a diameter of about 1 cm. and separated by 2–3 cm. Current strength was adjusted, before ischaemia began, to give the maximal amplitude of recorded muscle action-potential. The shock repetition rate was usually 1/sec., and the stimulating pulse triggered the sweep of the C.R.O. In some experiments a slowly rising current was used as stimulus, with the active cathode over the nerve (Kugelberg and Skoglund, 1946).

Ischaemia was produced by means of pneumatic cuffs, 10 cm. in width. On the upper arm the pressure was 200 mm. Hg., and on the forearm 250 to 300 mm. Hg.

Results

Stimulation by Brief Shocks.—It was unnecessary in these experiments, and in fact a disadvantage, to maintain ischaemia until blocking of the ulnar nerve, indicated by loss of voluntary contraction, had occurred; it usually begins after about 20 minutes and may be complete in 30. In the subject illustrated (Fig. 1) lively repetitive responses occurred on release from ischaemia which had lasted only 14 minutes.

To decide from which part of the neuro-muscular apparatus the repetitive action-potentials arise one of the experiments of Magladery and others (1950) was repeated, whereby, with two occluding cuffs, the blood flow could be restored to the proximal part of the upper arm, while the more peripheral stretch of nerve and the muscle remained ischaemic. One cuff (A) was placed as high as possible on the arm and the second cuff (B) just above the elbow, with the stimulating electrodes between them, over the ulnar nerve. Shock stimulation, before ischaemia began, gave rise to a direct volley in the first interosseous muscle with a latency of 12 msec. followed by a smaller discharge with an approximate latency of 26 msec.

(The latter is the F wave of Magladery and others, and is evidently a central response set up by the ascending nerve volley; whether it is a reflex, as they hold, or the secondary discharge in antidromically excited motor neurones described by Renshaw (1941), is immaterial to the present study, and we shall use Magladery's uncontroversial term.)

The circulation in the whole arm was stopped by the inflation of cuff A ; just before its release, after 14 minutes, cuff B was inflated so that the forearm and hand should remain ischaemic. At about this time the nerve was stimulated again, with a similar result, except that the latencies were somewhat increased, probably due to cooling. On stimulating three minutes later, however, the direct volley was followed by a long-lasting, repetitive discharge, detectable after a latency of 21 msec. (Fig. 1B and C). Thus it began before the expected time of the F wave and could not have been a spinal cord reflex. Since the muscle, neuromuscular junctions, and distal stretch of nerve were still ischaemic this experiment indicates clearly that the post-ischaemic nerve can give rise to repetitive action-potentials.

The above conditions, with both cuffs on the upper arm, are not ideal for the experiment as different subjects show considerable variation in the readiness with which a repetitive discharge is produced. In some ischaemia for 14 minutes is insufficient, while with longer periods nerve-block may develop below cuff B, so that little of the evoked direct response and subsequent repetitive discharge may pass through. Since blocking is more pronounced in the proximal part of the nerve (Lewis, Pickering, and Rothschild, 1931), it is more easily avoided if the lower cuff is placed more distally, on the forearm. Objections, to be discussed later, have been made to the use of forearm cuffs, for which reason we have described first the results obtained with both cuffs on the upper arm. Placing the second cuff on the forearm, however, enables repetitive responses to be obtained more readily and consistently. The following experiment of this type confirms the previous findings and also demonstrates a characteristic of the repetitive response, previously described as a pseudo-reflex (Kugelberg, 1946a).

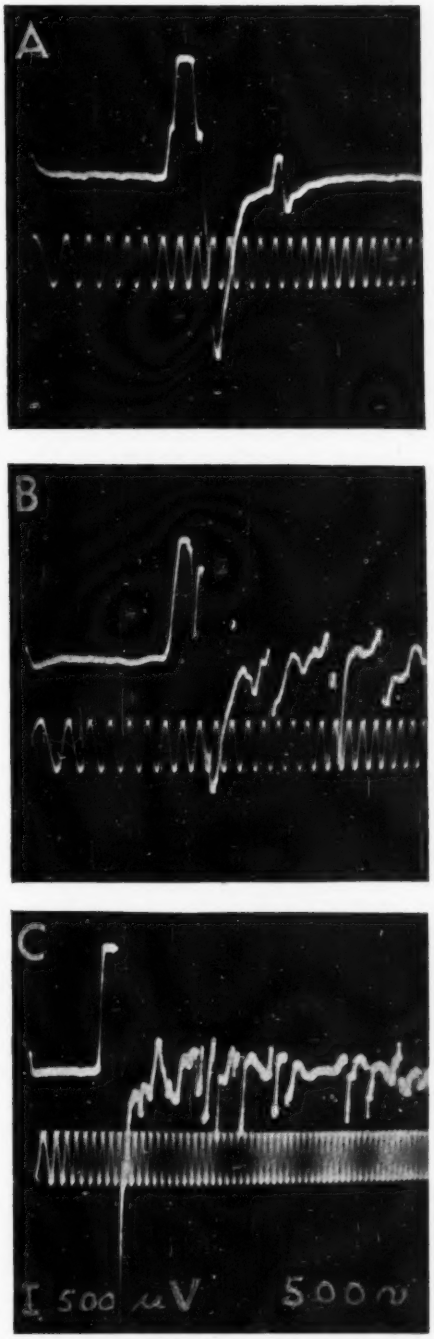

FIG. 1.—A. Single shock stimulation caused a large diphasic response with a latency of 12 msec. followed by a smaller (F) wave at 26 msec. B and C. Cuff A, high on the upper arm, has been inflated ; just before its release cuff B, immediately above the elbow, has been inflated. The direct response to shock stimulation, three minutes after release of A, is followed by a repetitive response.

One cuff was placed on the upper arm and inflated for 20 minutes, a second cuff on the forearm being inflated just before the release of the first. On stimulating the ulnar nerve at the elbow before ischaemia the direct response occurred after 8·5 msec. followed by a small F wave at 26 msec. (Fig. 2A), while when the nerve was stimulated at the wrist the latencies were 3 and 31 msec. respectively (Fig. 2B). From one half to seven minutes after the release of the cupper cuff stimulation at the elbow evoked a prolonged repetitive response which immediately followed the direct volley (Fig. 2C). With stimulation at the wrist the repetitive discharge was delayed and followed the direct volley after a free interval in the case illustrated, with a latent period about the same as that of the F wave (Fig. 2D), though in other cases it appeared somewhat earlier, evidently unrelated to the F response. The lower cuff was released when, seven minutes after release of the upper, the repetitive discharge had subsided (Figs. 2E and F) ; shortly afterwards it began again, but without a free interval between it and the primary response,

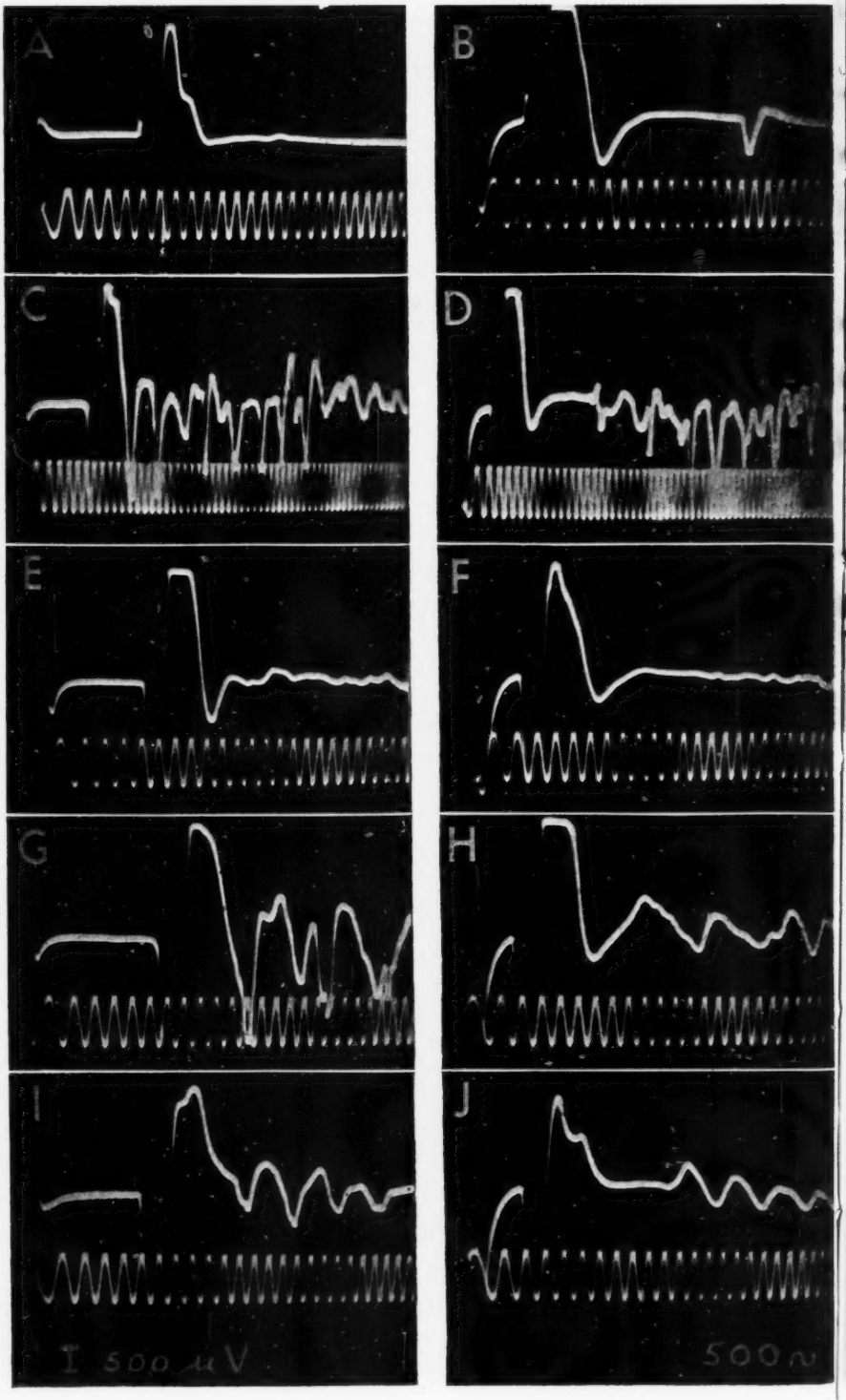

FIG. 2.—A. Stimulation of the ulnar nerve at the elbow causes a direct response from first dorsal interosseous with a latency of 8·5 msec., followed by a small F wave at 26 msec.

B. With stimulation at the wrist the latencies are 3 msec. and 31 msec.

C. Cuff A has been inflated on the upper arm for 20 minutes ; just before its release cuff B on the forearm has been inflated. From half to seven minutes later each direct response to a shock at the elbow is followed immediately by a repetitive discharge.

D. On stimulation at the wrist the direct response is followed by a repetitive discharge with a latency of 27 msec., leaving a silent interval between them.

E. Seven minutes after release of cuff A there is no longer an after-discharge when stimulating at the elbow or, F, at the wrist.

G. Shortly after release of cuff B, 27 minutes from the beginning of the experiment, repetitive after-discharge returns on stimulating at the elbow, and H, also at the wrist, but now without a silent interval.

I. After a further five minutes the repetitive discharge still follows the direct response to a stimulus at the elbow, but at the wrist, J, the silent interval has returned.

whether stimulation was at the elbow (Fig. 2G) or at the wrist (Fig. 2H). After a further five minutes, before it finally subsided, although there was no free interval between direct and repetitive responses when stimulating at the elbow (Fig. 2I), an increasingly long interval occurred when stimulating at the wrist (Fig. 2J).

This sequence of events again shows that it is motor nerve fibres in the post-ischaemic state which respond rhythmically, since the distal structures were still ischaemic when the repetitive discharge was evoked by proximal stimulation after release of the upper cuff. The free interval before the repetitive discharge evoked by distal stimulation

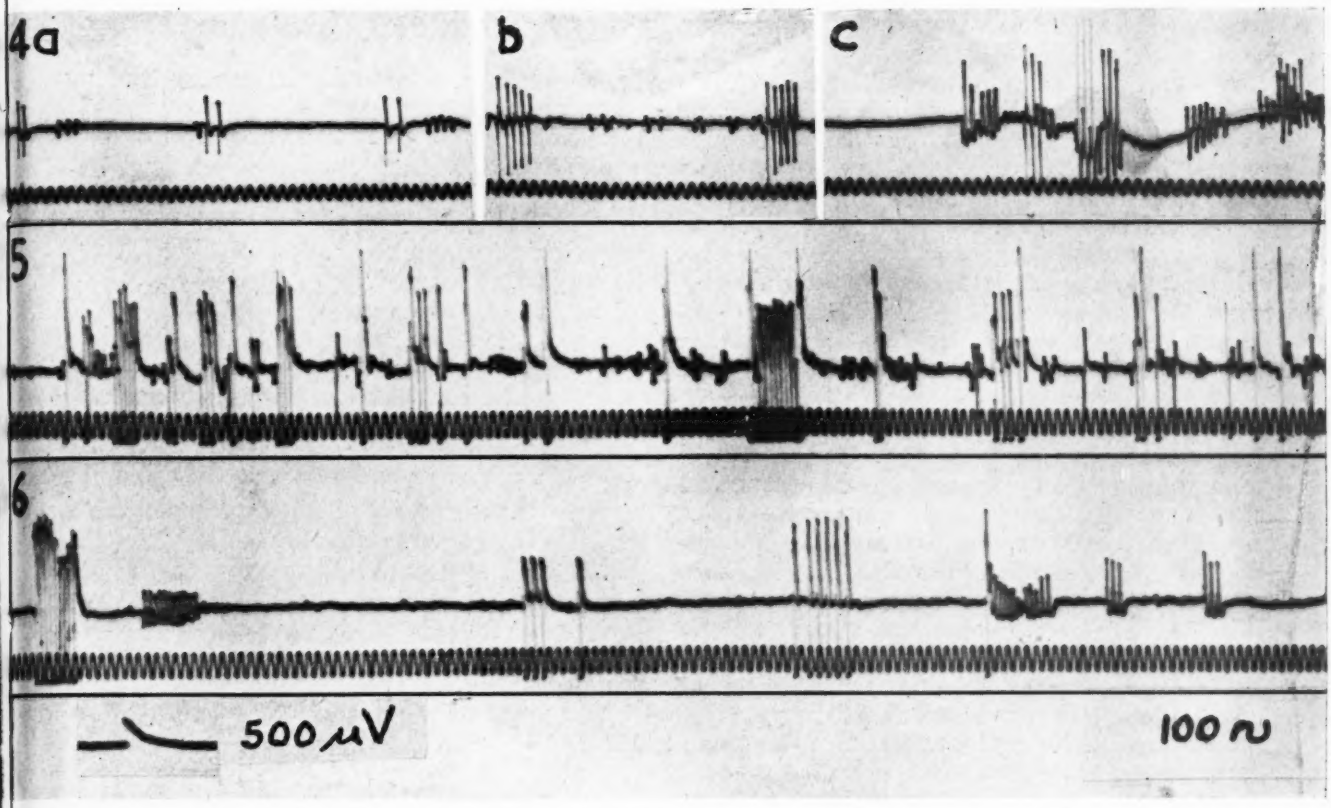

FIG. 4.—Cuff A has been inflated on the upper arm for 20 minutes ; just before its release cuff B on the forearm has been inflated.

A. Cathodal stimulation of the ulnar nerve at the elbow by a slowly rising current causes double or treble responses, or B, more prolonged bursts.

C. Sudden reduction of the current strength causes fresh repetitive outbursts.

FIG. 5.—With two cuffs on the upper arm, after release only of the more proximal, many of the action potentials of a voluntary contraction are followed by a repetitive after-discharge.

FIG. 6.—From the same experiment as Fig. 5. Repetitive action potentials occur spontaneously accompanying fascicular twitching of the muscle.

can be accounted for by the time taken for the antidromic volley, inevitably evoked by stimulation, to reach the post-ischaemic stretch of nerve, and there start a repetitive discharge, sent back as a pseudo-reflex (Kugelberg, 1946a). After release of the lower cuff the distal structures became post-ischaemic, and the repetitive discharge then followed the direct volley with little or no free interval. The reappearance of the pseudo-reflex, however, when repetition began to subside, indicates that a proximal stretch of nerve retains its property of rhythmic response longer than a more distal one.

Stimulation by Slowly Rising Current and Voluntary Contraction.—Stimulation of the ulnar nerve in the post-ischaemic state by a slowly rising current gave rise to rapidly repeated responses from single motor units. With both cuffs above the elbow, or better, for the reasons given above, with one cuff on the forearm, after release of the upper cuff stimulation at the elbow gave rise to double or treble responses (Fig. 4A). or to longer bursts of responses (Fig. 4B). On sharply decreasing the current a further repetitive discharge was evoked (Fig. 4C).

With the same arrangement of cuffs a slight voluntary effort also gave rise to rapid rhythmic outbursts (Fig. 5) ; they were most pronounced at the beginning of the contraction, doubtless due to later fatigue of the trigger mechanism.

Spontaneous Repetitive Discharges.—Complete release of a limb from ischaemia regularly results in spontaneous repetitive discharges ; Magladery and others, however, did not find this to be the case when only 12 cm. of nerve in the upper arm were released after 30 minutes or after the abolition of voluntary movement. Even so, with a suitable choice of subject, repetitive discharges may occur under these conditions, as illustrated in Fig. 6. The bursts of repetitive action potentials were accompanied by rather slow fascicular twitches of

the muscle; these were also observed by Reid (1931), who assumed that they were caused by direct stimulation of the muscle. Their relationship to the return of circulation to the nerve rather than to the muscle was shown earlier (Kugelberg, 1944) and is illustrated again by the experiments described above.

Magladery and others (1950) state that the action potentials which accompany spontaneous contractions of the muscle in the post-ischaemic state are the result of spinal cord reflexes elicited by afferent discharges arising in distal structures. The pattern of discharge, in the records published by these authors, has not the same appearance as that accompanying the fasciculations studied here, and further, we found that blocking the ulnar nerve at the elbow, performed in one instance, did not abolish them. An injection of 10 c.cm. of 2% xylocain with adrenaline was given intraneurally, and the block proved effective in that 10 minutes before and after release of the cuff no action-potentials appeared either on maximal voluntary contraction, or on shock stimulation of the nerve proximal to the elbow. In this case the interosseous muscle had no supplementary innervation from the median nerve, tested by stimulating the nerve and recording from the muscle. The cuff on the upper arm, just above the elbow, was released after 25 minutes' inflation and this release was followed by spontaneous repetitive activity which could not, in the circumstances, be of reflex causation.

The Use of Cuffs on the Forearm.—The results obtained by Lewis and others (1931) and Merrington and Nathan (1949) on post-ischaemic sensory disturbances after compression of the forearm, have been criticized by Weddell and Sinclair (1947) and Magladery and others (1950) on the ground that there is a risk of leakage past the cuff. The latter workers observed at surgical operations on the hand that a cuff-pressure of 140–150 mm. Hg. on the upper arm was sufficient to prevent oozing, whereas a pressure of 60–70 mm. Hg. greater was required on the forearm for the same purpose. They went so far as to say " that any interpretation of the results of cuff pressure in the forearm which assume complete arrest of circulation must be discounted ". It is a simple matter to use, as we

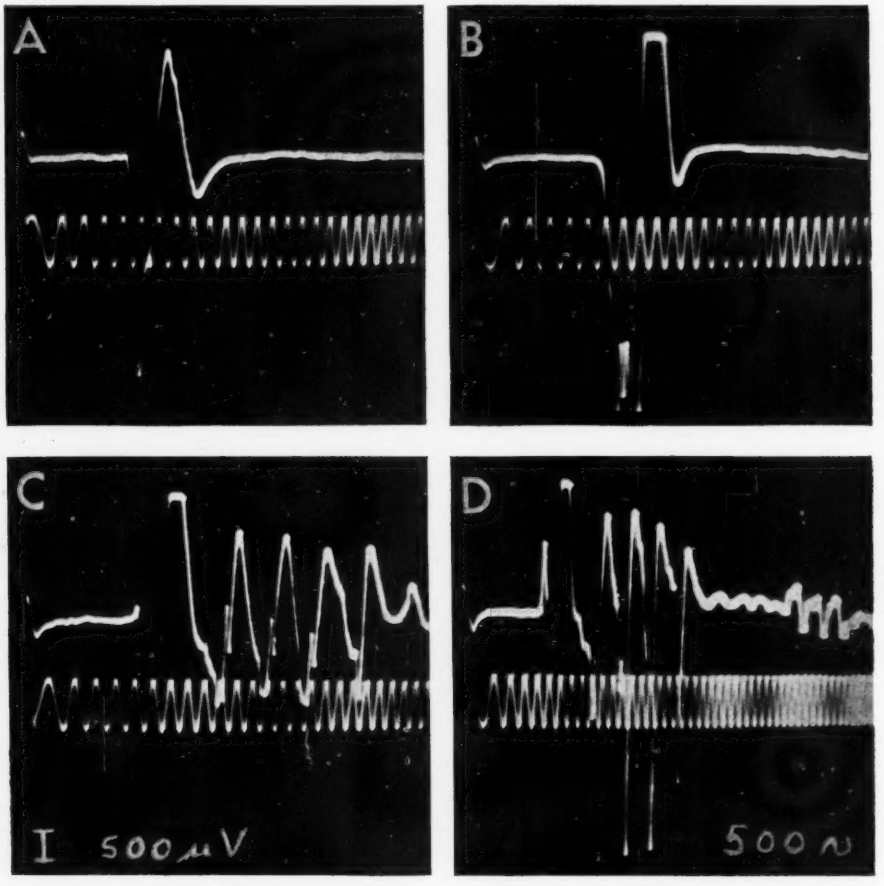

FIG. 3.—A. A single shock to the ulnar nerve at the elbow causes a direct response from the first dorsal interosseous muscle with a latency of 8·5 msec.

B. A cuff has been inflated on the upper arm and after 17 minutes the pressure has been lowered sufficiently for the pulse to become perceptible at the ante-cubital fossa and at the wrist. On stimulation the direct response has an increased latency but there is no repetitive after-discharge.

C and D. After complete release of the cuff six minutes later a repetitive after-discharge follows each direct response.

did, a pressure of 250–300 mm. Hg. in all forearm cuffs, though it can be shown that, at least for the repetitive response, this is an unnecessary precaution, as the following experiment illustrates.

A cuff was placed proximally on the upper arm and inflated to 200 mm. Hg. Stimulation of the ulnar nerve at the elbow before the beginning of ischaemia evoked a direct response with a latency of 8·5 msec. (Fig. 3A). After compression for 17 minutes the pressure was lowered sufficiently for the pulse to be clearly perceptible in the ante-cubital fossa (on auscultation), and at the wrist. During the following six minutes, though no appreciable block had developed, no repetitive response could be elicited on stimulation (Fig 3B). Thirty seconds after the pressure had been fully released, however, the muscle responded with synchronized repetitive discharges, at intervals of about 7 msec. (Figs. 3C and D). Stimulation of the ulnar nerve of the other arm, used for reference, after the total release of pressure following compression for 17 minutes, evoked a lively repetitive response. Thus, much greater leakage than that which might occur past a forearm cuff at a pressure of 250–300 mm. Hg. did not give rise to repetitive discharges. We consider that our experiments cannot be considered invalid because of the use of forearm cuffs.

Discussion

Both induced and spontaneous repetitive discharges in the first phase of the post-ischaemic state evidently have their origin in motor nerve fibres, though not necessarily in these alone. If the period of ischaemia has been sufficiently long the whole stretch of nerve responds in this manner. No attempt was made to investigate quantitative differences between distal and proximal stretches of nerve, although the frequent occurrence of a pseudo-reflex on stimulating at the wrist does not point to an excess of repetitive tendency in distal nerve fibres, but rather to the contrary.

Repetitive firing during the post-ischaemic state is correlated with large changes in the excitability of motor nerve fibres ; that is, with hyperexcitability (lowered rheobase), and the breakdown of accommodation (Kugelberg, 1944). These changes in both repetitive tendency and excitability are greatly augmented by hyperventilation and hypocalcaemia, and diminished by hypercapnia and hypercalcaemia (Kugelberg, 1944 ; 1946 a and b ; 1948 ; Gernandt and Zotterman, 1946). This relationship to changes in the ionic environment of nerve may explain the rather large variations in the reaction to ischaemia and post-ischaemia among normal individuals, which complicate the experimental conditions, and may account for some of the discrepant opinions of different authors regarding the mechanisms concerned.

On the sensory side the rhythmic high-frequency (100–200 p.s.) discharge in motor nerve fibres, occurring spontaneously or induced by action potentials which enter the hyperexcitable stretch of nerve, has its counterpart in the post-ischaemic paraesthesiae, which are intensified by touch or other stimulation of the skin. The results obtained on the motor side are in agreement with the opinions of Lewis and others (1931), Zotterman (1933), Gordon (1948), and Merrington and Nathan (1949), that the pins and needles have their origin in sensory nerve fibres and not at the nerve endings, as suggested by Weddell and Sinclair (1947), and by Magladery and others (1950).

Summary

The repetitive discharges in muscle which occur after the release of a limb from ischaemia have been variously considered as arising in proximal nerve or in distal structures, particularly the myoneural junctions.

When two pneumatic cuffs were inflated on the upper arm and, after a suitable interval, only the upper cuff was released, a repetitive discharge occurred in the first dorsal interosseous muscle following shock stimulation of the ulnar nerve. The distal stretch of nerve and the muscle were still ischaemic, so that the repetitive tendency must have developed in that stretch of nerve which had been released from ischaemia.

With the same arrangement of cuffs repetitive discharges occurred in response to a slowly increasing electrical stimulus or to voluntary contraction of the muscle, and also spontaneously.

Owing to individual variations in the onset of ischaemic nerve block and post-ischaemic repetition, as well as to the fact that nerve block occurs more readily in proximal nerve, more consistent results are obtained when one cuff of the pair is on the forearm. Objections to this arrangement are discussed and countered by experimental evidence.

The possibility of spontaneous repetitive discharges being of reflex causation is discounted by blocking the ulnar nerve in the ischaemic area with xylocain.

The bearing of these observations on the parallel post-ischaemic sensory phenomena is discussed.

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NEUROMUSCULAR DISORDERS AMENABLE TO WHEAT GERM OIL THERAPY

BY

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There has been a natural desire to find some neuromuscular disorder in man equivalent to the nutritional muscular dystrophy which occurs in animals deprived of wheat germ factors or of vitamin E. So far the search has been unsuccessful. Our own therapeutic trials of wheat germ oil were begun in 1936, and since that time 107 patients, most of them with neuromuscular disorders, have been studied. In each case treatment has been carried out over many months, and in some cases for many years.

In certain conditions, for example, progressive motor neuron disease, no favourable effect has been noted. In 12 patients with other disorders improvement or recovery has been sufficiently dramatic to make us believe that treatment was responsible. These conditions include dermatomyositis, menopausal muscular dystrophy, and some cases of progressive muscular dystrophy.

Review of the Literature

Evans and Bishop (1922) found that female rats deprived of certain foodstuffs were unable to carry on normal gestation. The factor necessary to prevent abortion was found plentifully in green vegetables, cereals and seeds, and especially in wheat germ oil. It was tentatively named vitamin X and later vitamin E. It has become popularly known as the "anti-sterility vitamin", although the latter term is far too inclusive.

Emerson, Emerson, and Evans (1936) identified this factor as alphatocopherol, and later Karrer and Demole (1938) synthesized it. Evans and Burr (1928) observed that the offspring of female rats partially deprived of vitamin E often became paralysed toward the end of lactation. It remained for Olcott (1938) to show that the symptoms were due to widespread necrosis and dystrophy in the voluntary muscles. Although some terminal neurites may be destroyed in advanced cases, as shown by Telford (1941), the process affects the muscles primarily. A single dose of 0·5 mg. of natural or synthetic tocopherol provides complete protection according to a number of workers cited by Pappenheimer (1943).

Einarson and Ringsted (1938) made an early and extensive study of this condition. In addition to the muscular changes, they described degeneration of the posterior columns and anterior horn cells of the spinal cord, with resultant neural muscular atrophy. More recently, Luttrell and Mason (1949) and Malamud, Nelson, and Evans (1949) have confirmed the eventual occurrence of neural lesions in vitamin E-deficient rats. Other workers, notably Pappenheimer (1943), have been impressed with the primary muscular involvement in the disorder. Different animals show varying kinds and degrees of pathology but most seem to be susceptible, including rats, mice, rabbits, guinea-pigs, ducklings, and dogs.

Pappenheimer has summarized the pathological changes to be found in the affected muscles. The lesions are widespread but not necessarily symmetrical, and they may not affect an individual muscle in its entirety. In the acute form there is extreme hyaline necrosis with swelling and loss of cross striations. Oedema and a violent cellular reaction may occur. Sarcolemmal nuclei multiply by mitosis and form new myofibrils with every evidence of regeneration. In chronic cases there is a gradual replacement of muscle fibres with fat and fibrous tissue, giving a picture indistinguishable from that of human pseudohypertrophic muscular dystrophy.

From the biochemical viewpoint creatinuria is an outstanding feature, and it is diminished by the administration of tocopherols (Mackenzie and McCollum, 1940). It has also been found that both *in vivo* and *in vitro* dystrophic muscle has an

abnormally high oxygen consumption, and this is corrected by the addition of alpha-tocopherol (Victor, 1934; Madsen, 1936; Pappenheimer, 1943). Interestingly enough, Brinkhous and Warner (1941) have also shown that dystrophy can be produced in dogs by making a biliary fistula. Here the animals received a normal diet, but diversion of bile apparently interfered with absorption of the fat-soluble vitamin E.

All these findings naturally suggested the trial of vitamin E in a number of human neuromuscular disorders of unknown origin. A flurry of contradictory papers soon appeared. Typical of the early, optimistic reports were those of Wechsler (1940), Bicknell (1940), and Stone (1940). Studies published later, such as those of Doyle and Merritt (1941) and Alpers, Gaskill, and Cantarow (1941) failed to support the early claims.

Materials and Methods

We report here a long term study of the effect of wheat germ oil in the treatment of 107 patients. The majority suffered from neuromuscular disorders. A breakdown of this material will be found in Table I. Diagnosis was made primarily on careful clinical examination, but special techniques were used in most cases. These included tests of muscle strength and fatiguability, estimations of creatinuria during a meat-free dietary regime, electromyograms, and muscle biopsy examinations. Details of these methods have been described elsewhere (McEachern and Rabinovitch, 1950).

The wheat germ oil used for all cases was supplied by Viobin (Canada) Limited. Their assays claim 2·5 to 3·0 mg. of mixed tocopherols per g. (1·1 ml.). The usual dosage was dr. 2 t.i.d. for adults and dr. 1 t.i.d. for children. Since 1 dr. is about 3·9 g. of wheat germ oil the usual daily dose of tocopherols was 65 mg. for adults and 33 mg. for children. This was supplemented in some cases by alphatocopherol acetate ('ephynal' from Roche) and by wheat germ oil concentrated for tocopherols ('phytopherol' from British Drug Houses; 'germol' E from Ayerst, McKenna, and Harrison). Wheat germ oil concentrate 10 : 1 (Viobin Corporation, Monticello, Illinois), prepared after the method of Milhorat and Bartels (1945), was used as a supplement in some cases. The tocopherol content of this concentrate, as described by the processor, is said to be slightly higher than that of the original wheat germ oil, viz. 3 to 3·5 mg. per g. Just what factors are enhanced by the 10 : 1 concentration is not clear. In any event, supplements of some of the above raised the daily intake of tocopherols to 300 mg. per day in a few cases. No correlation of effective therapeutic results and tocopherol intake could be noted on this basis, and the results have to be considered in terms of the basic addition of wheat germ oil to the dietary.

Until more is known about the factors in wheat germ oil effective against human disease no claims should be made for individual elements of it without good proof. Even vitamin E itself is a complex containing several tocopherols. If the lesson of the vitamin B complex family is kept in mind this point should be clear.

Results

Cases Unresponsive to Therapy.—These number 93 out of 107 cases and are listed in Table I. They include all cases of typical progressive motor neuron disease, of myasthenia gravis, of disseminated sclerosis, and a number of other conditions. No favourable response was found in these cases.

Cases Responsive to Therapy.—These include cases of atypical muscular atrophy, progressive muscular dystrophy, menopausal muscular dystrophy, and dermatomyositis.

Atypical Muscular Atrophy.—In the two patients who did show improvement several factors seem to be pertinent. They suggest that a condition other than progressive muscular atrophy prevailed, despite the localized weakness and wasting suggestive of this syndrome.

In case No. 1 bilateral wasting of the forearm and hand muscles appeared rapidly at the age of 20 and remained stationary for 20 years. In the past two years progressive weakness, without wasting, has developed in the lower extremities, coinciding with the onset of the menopause. It may be that the signs in the upper extremities were residues of poliomyelitis, and that the present troubles in the lower extremities are due to superadded menopausal muscular dystrophy.

Case No. 2 presents similar features. Poliomyelitis could account for the long-standing and localized weakness and atrophy. A recent improvement of muscle power in the lower limbs, together with the reduction of fasciculations, is against the diagnosis of progressive muscular atrophy.

CASE NO. 1 (M.N.I. 48–5852, D. D., woman, aged 40).—The patient complained of weakness in the lower limbs, slowly progressive for two years. There was pre-existing marked weakness of the upper extremities with a claw hand deformity which had developed fairly rapidly at the age of 20. Menses recently had been irregular and scanty.

On examination, weakness and wasting, marked in the hand and forearm muscles, moderate in the arm and shoulder muscles bilaterally, was apparent, and also weakness in dorsiflexion of the foot and flexion of the legs. Deep tendon reflexes were absent. Biopsy of the right brachio-radialis showed atrophy of fibres, an increase in the number of sarcolemmal nuclei, connective tissue replacement, and thickening of blood vessels.

TABLE I

PATIENTS INVESTIGATED IN THE NEUROMUSCULAR DISEASE CLINIC

Diagnosis	Cases Investigated	Cases Treated with Wheat Germ Oil	Results
Cases Improved			
Atypical muscular atrophy	2	2	2 improved
Progressive muscular dystrophy	29	25	5 ,,
Menopausal muscular dystrophy	7	5	3 ,,
Dermatomyositis	3	3	3 ,,
Cases not Improved			
Progressive muscular atrophy	16	11	Not improved
Amyotrophic lateral sclerosis	20	14	,, ,,
Progressive bulbar palsy	1	1	,, ,,
Motor neuronitis	3	3	,, ,,
Myasthenia gravis	24	11	,, ,,
Myotonia congenita	2	2	,, ,,
Myotonia atrophica	2	0	,, ,,
Peroneal muscular atrophy	1	1	,, ,,
Thyrotoxic myopathy	1	0	,, ,,
Dystonia musculorum deformans	1	1	,, ,,
Friedreich's ataxia	2	2	,, ,,
Obliterative arterial disease	3	1	,, ,,
Disseminated sclerosis	9	9	,, ,,
Unclassified myopathies	25	16	,, ,,
Total	151	107	

Biopsy of the left gastrocnemius showed variation in size and shape of the fibres, with some loss of cross striation and areas of increased nuclei. An electromyogram showed fairly normal potentials from the right arm and hand muscles, without fibrillation but with large areas of silence. In the left tibialis anticus there were complex motor units and areas of denervation fibrillation. In the right tibialis anticus extremely high voltage motor units and disintegrated motor units were observed.

Wheat germ oil concentrate, dr. 2 t.i.d., was prescribed. After two months there was marked improvement of the leg weakness, and this improvement has persisted for six months. There is no change in the weakness or atrophy of the upper extremities.

CASE NO. 2 (M.N.I. 41–7196, S. L., woman, aged 50). —The patient had had poliomyelitis in childhood with weakness and atrophy of the right upper and left lower extremities. She had suffered from generalized fasciculations for eight years, and generalized weakness, nervousness, numbness and tingling in the hands and fingers for one year. Menses had been irregular and scanty for one year.

Examination showed weakness and atrophy of the right shoulder and arm, of both hands and of the left leg muscles. Reflexes were diminished in the right upper and left lower extremities, and there were fasciculations in both lower extremities. Blood pressure was 200/120. Fasciculations were active in the leg muscles. An E.M.G. showed no denervation fibrillation.

Wheat germ oil, dr. 1 t.i.d., was given. Within three months there was improvement of all complaints and this persisted for 18 months. Fasciculations were only faintly visible. Wheat germ oil was discontinued for several months but was begun again when leg weakness reappeared. Improvement was maintained for four years of continuous dosage, but relapse then set in despite the continuance of therapy.

Progressive Muscular Dystrophy.—Five of the 25 patients treated showed sufficient improvement to warrant continuation of treatment with wheat germ oil. In these five patients symptoms appeared in three at about walking age, and in the two others at about the age of 14. In all five there was involvement of the pelvic girdle muscles, and in one the pectoral girdle was also involved. Although no family history could be elicited, the clinical and laboratory findings agreed with the classical descriptions of progressive muscular dystrophy. Evidence of arrest of the disability with moderate improvement in locomotion seemed quite clear.

CASE NO. 1 (O.P.D. 282979, R. T., boy, aged 22 months). —The patient's mother told of his inability to rise from the sitting position. Birth had been normal and also development up to the age of 14 months, at which time he began walking. The mother observed that the child " climbed up his legs " to assume the erect position.

On examination the patient appeared to be a normal child in every respect save for the clumsy manner of rising to his feet. There was " duck-waddle " gait, rubbery consistency of the calf muscles, and absence of all tendon reflexes.

Wheat germ oil concentrate, dr. 1 q.d., for two months was given, then changed to wheat germ oil, dr. 3 q.d. There was slow improvement, first noticeable two months after treatment began. Eighteen months later he could rise rapidly from the floor, still using his hands. He could walk and run unaided. The " waddle " was less pronounced, and he climbed stairs. The calf muscles were not so rubbery but reflexes were still absent.

CASE NO. 2 (O.P.D. G–587, T. K., boy, aged 7).—The child had an abnormal gait since starting to walk, and difficulty in climbing stairs or getting up from a chair.

On examination the patient seemed a well-developed boy who walked with a wide base and a waddling gait. He had difficulty in standing without pushing on his thighs. The calf muscles were of a moderately rubbery consistency.

Wheat germ oil concentrate, dr. 1½ q.d., was ordered. Improvement in ability to climb stairs and to rise from the floor was noticeable within two months. The improvement persists.

CASE NO. 3 (O.P.D. G–6856, A. O'C., boy, aged 7).—The child had a clumsy walk, and difficulty in climbing stairs since the age of 4½.

On examination it was seen that his walking was fair but he ran on tiptoe. Rising from the floor and climbing stairs was very difficult. There was no atrophy, hypertrophy, or fasciculation of muscles. An electromyogram was normal.

Wheat germ oil concentrate, dr. 3 q.d., was ordered. Improvement was seen within two months and has persisted for seven months. Rising from the floor, walking, running, and climbing stairs were performed more smoothly, and the child experienced less fatigue on effort. He rides a bicycle without difficulty.

CASE NO. 4 (O.P.D. G–3434, E. M., man, aged 18).—The patient complained of progressive wasting of the arms and thighs bilaterally for four years following severe scarlet fever. Weakness was first apparent in the lower limbs with frequent falling. He had had articular pain since scarlet fever.

On examination marked weakness bilaterally of the deltoids, biceps, triceps, rhomboids, sacrospinalis, and quadriceps muscles was noted. Wasting was evident in both pectoral and pelvic girdle muscle groups, most marked in the former. All the deep tendon reflexes were absent. There was no hereditary factor. From a muscle biopsy of the right rectus femoris the muscle appeared soft, flabby, avascular, and microscopically the muscle fibres were seen to be unequal in diameter. Cross striations were normal but the number of sarcolemmal nuclei was increased. The capillary network was poorly developed. Many of the medium sized vessels showed proliferation of the medial coat and some of adventitial coverings.

Wheat germ oil concentrate, dr. 4 q.d., was given. After six months of treatment there was an improvement in strength. The patient did not fall, and had been able to do gardening all summer. Objective tests showed definite improvement.

CASE NO. 5 (O.P.D. G–6417, G. L., man, aged 28).—The patient said that since the age of 13 he had noticed gradual weakness and wasting of the thigh muscles, clumsiness in walking, and difficulty in rising from the floor from the seated position and in climbing stairs.

Examination showed marked atrophy of the thigh muscles with pseudohypertrophy of calf muscles bilaterally. The thigh flexors were weakest. Muscle biopsy of the right rectus femoris showed hard, dense tissue made up of muscle fibres which had undergone hyalin degeneration. There was marked increase in connective tissue and fat, and in the capillary network. The variation in diameter of muscle fibres was marked, and there was evidence of lymphocytic infiltration. An electromyogram recorded many multiple, low voltage short duration units, with large portions of muscle electrically silent, but no evidence of denervation fibrillation.

Wheat germ oil concentrate, dr. 6 q.d., was ordered. Within one month there was improvement in strength, in ability to walk, and to climb stairs. Treatment has been continued for eight months and improvement continues.

Menopausal Muscular Dystrophy.—These patients are described in the following paper, also several other patients with the same condition who responded to cortisone.

Dermatomyositis.—Lépine (1901) first conceived the idea that dermatomyositis may be primarily a disturbance of the blood vessels. Since then opinions have varied as to the nature of the cutaneous and muscular changes observed. The skin is often glossy, seems to be slightly adherent to the underlying structures, and there may be scaling and evidence of atrophy. Muscular changes may be profound.

Banks (1941) sought a common denominator in scleroderma, disseminated lupus erythematosis, the Libman-Sacks syndrome, and polyarteritis nodosa. This view is receiving attention now because of the effect of cortisone upon these conditions. Clinical improvement and marked reduction of creatinuria was obtained by Milhorat, Weber, and Toscani (1940) in two cases treated with 125 g. of whole wheat germ daily. In a later report by Milhorat, Toscani, and Bartels (1945) creatinuria in three patients with dermatomyositis was reduced by the administration of large amounts of fresh wheat germ. It is important to note that rigorous control of the samples of wheat germ obtained from different sources showed considerable variation in their effects. These authors believe that the effects of wheat germ oil may be dependent upon its method of preparation.

Muscle biopsy findings in dermatomyositis have been reported by Silverman and Powell (1945). They observed an increase in sarcolemmal nuclei,

infiltration of the interstitial stroma with plasma cells and with small round cells, occasional neutrophils, and phagocytes. Sometimes there was infiltration of the walls of the medium sized vessels.

Three cases of dermatomyositis with generalized muscular weakness and a rubber-like consistency of muscles have been treated with alphatocopherol and wheat germ oil in this clinic. Marked improvement in symptoms and signs was obtained in all instances. In all three patients hyperthyroidism had existed, and in two of them thyroidectomy had been performed before the institution of therapy.

CASE NO. 1 (M.N.I. 5700, L. R., man, aged 62).—The patient complained of weakness of the legs, pain in the knees, and cramps in the feet and legs for four years.

Examination showed that the muscles of the forearms, thighs, and calves were firm to touch with skin adherent to the deep fascia. The small joints of the fingers were stiff. A subtotal thyroidectomy had been performed one year previously.

A total of 9·18 g. of alphatocopherol in 90 days was given by mouth and parenterally. After this the muscles were found to be less rubbery, stiffness was diminished, cramps less frequent, and sufficient strength had returned to enable the patient to return to work as a painter.

CASE NO. 2 (R.V.H. 41–4450, I.MCG., woman, aged 49).—The patient complained of generalized joint pains, tenderness, and limitation of movement of the right shoulder two months after thyroidectomy.

Examination showed generalized weakness and wasting of muscles, especially in the upper limbs, and a rubber-like induration of the subcutaneous tissues, muscles, and skin. The small joints of the right hand and left shoulder showed some fixation. A radiograph showed no bony changes. A neurological examination gave normal results. B.M.R. was plus 27%. There was some exophthalmos, and a few residual signs of hyperthyroidism persisted.

Wheat germ oil, dr. 3 q.d., was given. Improvement in symptoms was noted within two months. Eighteen months later it was found that the rubbery induration of subcutaneous tissues and muscles had disappeared completely. There was no swelling or limitation of joint movement, or obvious wasting or weakness of muscles.

CASE NO. 3 (M.N.I. 42–5504, M. F., woman, aged 47).—The patient complained of neck pain for three weeks, followed by weakness of the muscles of the neck and of the upper extremities for one year.

Examination showed marked thoracic kyphosis, marked atrophy of the pectoralis and trapezius groups and intrinsic muscles of the hands. The patient could not extend the head or hands. Deep tendon reflexes were absent in upper extremities. The skin was remarkably glossy, firm, inelastic, and adherent to the underlying structures.

Wheat germ oil, dr. 4 q.d., was given. There was definite improvement in the strength of the neck and arm muscles within two months. The skin became softer, less glossy, and less adherent to the underlying tissues. Improvement persisted for six years, after which she was again admitted to hospital with a diagnosis of chronic thyrotoxicosis with generalized osteoporosis, muscular atrophy, and scleroderma.

Discussion

It is not our desire to add to the confusion on the effects of wheat germ and vitamin E. Nevertheless, our experience indicates that certain neuromuscular disorders respond to wheat germ oil in a rather dramatic way. We have not used alphatocopherol alone, but it is possible that similar results might have been obtained with that substance. Nutritional muscular dystrophy in animals is prevented by crystalline alphatocopherol. In several of our cases relapse occurred upon withdrawing wheat germ oil, and improvement set in again when medication was resumed.

The conditions which respond most vividly might be grouped under the general term of collagen diseases, viz. dermatomyositis and menopausal muscular dystrophy. These are probably metabolic in nature rather than inflammatory, and their response to adrenal corticoids, as shown in the next paper, should provide a lead. It may be found that wheat germ factors and tocopherols are building blocks for steroid hormones, or that they contribute to their tissue effects.

One can only speculate upon the mechanism of progressive muscular dystrophy. It may be a metabolic disorder in which some congenital or acquired lack of essential enzyme systems leads to faulty nutrition of muscle. This could explain why overloading with a necessary food factor, e.g. wheat germ oil, might bring improvement in some cases. The work of Milhorat and Bartels (1945) suggested that patients with progressive muscular dystrophy might have a fault of digestion of vitamin E, and that the latter has to be changed or conjugated to produce the anti-dystrophic principle. If this is so, then the treatment of patients with alphatocopherol by the parenteral route might be expected to be ineffective too. It has been shown by a number of workers, including Mackenzie and McCollum (1940), that the feeding of tocopherols to animals with nutritional muscular dystrophy is much more effective than parenteral therapy. The latter workers give evidence, however, that this may be due to poor absorption of the oily solution from the tissues. Injection of the water soluble sodium phosphate of alphatocopherol was tried in two instances and produced prompt improvement. The author concluded that the activity of vitamin E in rabbit dystrophy is largely dependent upon its physical state.

It is evident from animal experiments that vitamin E is essential for the integrity of skeletal muscle. It is not so clear, however, what part this factor, or lack of it, plays in the biochemical processes of muscle. The most recent information on this point will be found in the symposium on vitamin E held before the New York Academy of Sciences (Ed. Mason, 1949). The recognition of even small groups of human cases responding to wheat germ factors or vitamin E will be of value in establishing the clinical picture of the deficiency in man.

Summary

One hundred and fifty-one cases of neuromuscular disorder have been investigated and followed for periods varying from many months to 12 years.

One hundred and seven of these patients were treated with either wheat germ oil or wheat germ oil concentrate, and sometimes with the addition of tocopherols. Thirteen showed definite improvement.

Improvement was noted in two cases of atypical muscular atrophy.

In five (three children and two adults) out of 25 patients with progressive muscular dystrophy, symptoms were arrested and moderate to marked improvement occurred.

Three out of five patients with menopausal muscular dystrophy showed remarkable improvement.

All three cases of dermatomyositis responded favourably to wheat germ oil therapy.

The conclusion is that certain neuromuscular disorders respond to wheat germ oil therapy. These conditions are ones which are also apt to show improvement with the administration of adrenal corticoids.

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THE CLINICAL FEATURES AND RESPONSE TO CORTISONE OF MENOPAUSAL MUSCULAR DYSTROPHY

BY

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We describe here a form of myopathy which occurs predominantly in women during the climacteric period or after, and appears to have characteristic features. The condition has been largely overlooked in the past. Its recognition is of special importance since improvement may occur during treatment with wheat germ oil or cortisone.

Our clinical experience is based upon a study of 12 patients, of whom 11 were women and one was a man. Six of the women were treated with wheat germ oil, and four showed notable improvement. The details are described in the preceding paper. Five patients, four women (two of them from the wheat germ oil series) and one man, have been treated with cortisone, with dramatic improvement in all instances. Details of the trial of cortisone in various neuromuscular disorders have been described in a previous paper (Shy, Brendler, Rabinovitch, and McEachern, 1950).

In this report we present the clinical features of this condition, together with pathological findings obtained by muscle biopsies. The use of maintenance doses of cortisone is also discussed.

Little reference to this condition can be found in the literature. Nevin (1936) described two cases of late dystrophy which were undoubtedly of this type. He also reviewed the literature. Other probable cases are noted in the communication by Bramwell (1922). The cases of late myopathy described by Barnes (1932) may be different. They occurred in families in which other members showed myopathic disorders at an early age.

Clinical Features

The typical picture is that of progressive weakness (sometimes rapid, sometimes slow) of the hip and shoulder girdle muscles. This leads to difficulty in ascending stairs or in rising from a chair without help from the arms. There is trouble, too, in raising the arms above the head, as in combing the hair, or in reaching up to high shelves. It progresses to the point where a waddling gait is evident, and the patient can no longer climb stairs. Unpredictable falls are common, and this symptom may precede all others by months or years. There is no warning and the legs just suddenly give way, although the patient may still be able to walk for many blocks on the level at this stage. There is no complaint of facial weakness, difficulty in swallowing or double vision, and power in the hands and feet remains normal.

Examination of the individual muscles reveals profound weakness of the iliopsoas muscles, the quadriceps femoris groups, the glutei, and the adductors of the lower extremities. In the upper extremities the supraspinati, the infraspinati, the deltoids, serratus magnus, triceps, and biceps are usually the most affected. On the whole, the lower extremities are more severely affected than the upper, but this may be a reflection of the greater weight bearing upon these structures. The condition may be so severe in the later stages that the affected muscles are not only powerless against resistance but against gravity alone. All of our patients have been examined by the method described in the monograph on peripheral nerve injury published by the Medical Research Council (1942).

Palpation reveals a "soft" consistency in the affected muscles. Visible wasting is unusual, perhaps because the patients are often well nourished, but occasionally the quadriceps femoris groups are seen to be atrophied.

Deep reflexes may be depressed in the muscles involved in proportion to the severity of involvement. Most of the muscles contributing to the usual reflexes are relatively unaffected, however, and the usual reflexes are therefore often lively. No signs of central nervous system involvement have been elicited. The thyroid is not enlarged, and the basal

metabolic rate is normal, in contrast to the low rates observed in juvenile dystrophy and dystrophia myotonica. Nevertheless a few of our patients have given a history of hyperthyroidism or of thyroidectomy in preceding years.

A gross increase in the ratio of creatine to the combined creatine and creatinine urinary output, as observed almost constantly in juvenile pseudohypertrophic dystrophy, is not a marked feature in these cases. Creatinuria is surprisingly small.

Other pathological disorders, gout and proliferative arthritis, were observed in two patients. The musculature affected, however, was not related to the affected joints.

Pathology

The picture is that of a dystrophy. We differentiate a dystrophic process from atrophy secondary to nerve degeneration by the following points: denervated muscle is affected in groups of fibres probably subserved by " motor units " ; dystrophic muscle, on the other hand, may show but a single abnormal fibre surrounded by histologically normal tissue. Necrosis with phagocytosis occurs in the more acute dystrophies, and cross striations are lost relatively early, whereas in neural atrophy striations may be present until late in the process. A large amount of fatty infiltration and replacement may eventually occur in dystrophic muscle, but not so commonly in the atrophic muscle. Hyalin changes, as seen by chromatic staining, have not been reliable indices of muscular dysfunction and they may indicate difficulty in fixation technique. Silver staining of nerve endings is of use in early cases. The muscle spindles, the interfusal fibres, are apparently spared in both dystrophies and neural atrophies.

At biopsy the muscle in the cases of menopausal dystrophy is usually pale. Biopsy has always been performed on the muscle most available and most affected clinically. Some muscles, e.g., iliopsoas, cannot be biopsied, but the nearest affected ones, e.g., quadriceps femoris, have then been chosen.

On microscopical examination* the main abnormality is patchy degeneration or necrosis of individual fibres, usually accompanied by phagocytosis of these portions. This process may affect but part of a muscle fibre, and the rest of it may be normal (Fig. 1). These areas are quite numerous and one need not search long to find them. Sometimes two such areas may be present in one low-power field (Fig. 2). There is usually proliferation of the sarcolemmal nuclei, and in some instances the only abnormality may be a central migration of the swollen sarcolemmal nuclei into the fibre. In advanced cases connective tissue elements and fat are predominant (Fig. 3). Aside from central migration of the nuclei, loss in cross striation is the earliest sign of muscle involvement.

When the dystrophy is of long standing, secondary changes are almost a constant finding. This is reflected in thickening of the media of the arterial walls. Occasionally some interstitial cellular response has been noted, but this is unusual as contrasted to states of dermatomyositis*.

Malamud, Nelson, and Evans (1949), Pappenheimer (1943a, 1943b) and others have described the pathology of vitamin E deficiency in *Rodentia*. This is a wide-spread dystrophic process with multiple areas of degeneration and necrosis. It is different from the dystrophies of human childhood, where necrosis is rare. Sections from patients with menopausal dystrophy, however, resemble those from the vitamin E-deficient animal. Necrosis is a common factor and it is relatively widespread in the involved muscles. Active phagocytosis is a characteristic of each, making such areas relatively easy to find on rapid scanning of the sections.

Cortisone : Laboratory Studies and Therapeutic Results

Cortisone was administered to five patients by the intramuscular route in a standard suspension of the acetate (25 mg. per ml.). No more than 50 mg. was administered in each depot. The first day of administration, 200 mg., or four depots, were used. Each successive day two depots (100 mg.) were administered, for an average duration of 21 days. The fall of circulating eosinophils in the blood was determined at daily and then at three-day intervals. Glucose tolerance curves were made at five-day intervals. The total urinary creatine and creatinine excretion was determined daily. The patients were all on a meat-free diet. Electromyograms were obtained in all five cases. Because of reports of electroencephalographic changes under ACTH therapy (Hoefer and Glaser, 1950), an initial electroencephalogram was obtained in each instance, and also one at the height of therapy. The muscle power of each patient was graded every two days. Where possible, muscle power was also tested by weight-pulley mechanisms, quantitative stair climbing, and ability to rise out of chairs of graded

* Sections of muscle removed were allowed to relax in isotonic saline for 20 minutes, and then placed in acidified zenkers. They were placed at a slight tension along the longitudinal axis by a weight tied to the distal end. Where possible both longitudinal and cross sections were cut.

Cross striations were studied by a light Mallory phosphotungstic acid stain, since it is believed that the myofibril and its disc are probably impregnated with this stain. Other sections were stained with haematoxylin and eosin, and haematoxylin and Van Gieson stain.

* In extreme cases one cannot distinguish menopausal dystrophy from other forms of advanced dystrophy.

FIG. 1 (× 240).—This demonstrates the breaking up of a portion of several fibres in an otherwise normal field. The cross-striations can be traced from the top of the section to the initial point of necrosis. Note aggregation of sarcoplasm and apparent phagocytic response.

FIG. 2 (× 550).—Focal necrosis is by no means rare. Here two fibres are affected in a single high-power field.

FIG. 3 (× 240).—Advanced dystrophy with fat and connective tissue replacement. At this stage the process cannot be distinguished from other types of muscle dystrophy.

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3

height. Patients were weighed daily, and blood pressure readings obtained twice daily.

By the fourth to sixth day of treatment all of these patients began to show marked improvement. The patient R.P. (Case 1), whose biopsy section is shown in Fig. 4, could, before treatment, ascend only three steps in 20 seconds by pulling herself with her arms. After two weeks she could mount 40 steps in 20 seconds without the use of her arms. All patients had a general euphoria and feeling of well-being. Sleeplessness was common, but not of the unpleasant kind. The experiment was terminated by substituting for the cortisone a suspension of cholesterol which resembled the cortisone in every detail. All patients began to relapse in about six days.

A marked fall in circulating eosinophils occurred in all cases. No marked change in the urinary creatine output was found. Glucose tolerance curves in all patients rose to high normal levels. Weight increased along with fluid retention, and was promptly lost by diuresis on lower dosages of cortisone. No toxic manifestations, such as hypertension, hirsutism, moon face, occurred. No change in the electroencephalogram was found in any of the five cases. Wound (biopsy) healing was delayed in some cases until the time of cholesterol control, and old operative and traumatic scars seemed to soften in texture.

Maintenance Therapy with Cortisone

For the past six months we have been faced with the problem of maintenance therapy : 100 to 150 mg. every two days approximates the optimum dosage in these cases. We have two patients on less medication and one on more than this amount. These patients are as dependent upon cortisone as are diabetics upon insulin. The prospect of a preparation which can be taken by mouth is very cheering to them.

The problem of fluid accumulation on the larger dosages becomes a real one. The patient receiving the most cortisone (200 mg. every two days) gained about 2 lb. weekly from excess fluid. We have recently placed her upon a low sodium diet with a fluid loss of 2 lb. weekly. To date we have had only two patients with this difficulty. It is recommended that the blood pressure, weight, and blood and urinary sugars be followed on all patients on maintenance therapy, at least for a time.

Case Reports

Case 1 (R. P., female, aged 52).—This patient was admitted with complaints of progressive weakness of the lower limbs of three years' duration. The onset was shortly after the menopause. This was accompanied by unpredictable falls, and by mild occipital and upper cervical aching.

No muscular atrophy was seen but the affected muscles felt soft. The chief muscular weakness lay in the quadriceps, iliopsoas, and the gluteus maximus muscles. Knee jerks were absent but achilles jerks were present. Reflexes in the upper extremities were quite brisk.

There was little abnormality in creatine output, the figures on three consecutive days before cortisone therapy being as follows :—

Urine Volume (ml.)	Specific Gravity	Creatinine (g./24 hrs.)	Creatine (g./24 hrs.)
1155	1·015	0·50	0·12
2050	1·012	0·62	0·11
1400	1·011	0·56	0·10

The glucose tolerance curve was within normal limits. Serum sodium was 320 mg.%, potassium 18·3 mg. %, chlorides 356 mg. %, and the carbon dioxide combining power was 43 volumes %.

This patient was placed on the usual cortisone regime. There was dramatic improvement as described above. Her weight increased on heavier dosage of cortisone and it had to be dropped for a period to 50 mg. daily. There was a sharp fall in the circulating eosinophils. No change could be noted in the serum potassium or sodium levels. The blood pressure did not rise appreciably. The muscle picture can be seen in Fig. 3. This shows multiple areas of isolated necrosis with loss of cross striations. There is also clumping of the sarcoplasm and disappearance of the sarcolemmal sheaths, and isolated atrophic degenerated fibres. There is a minimal interstitial histiocytic response.

Case 2 (B. M., aged 59).—Ten years ago this patient noted rapidly progressing weakness of the hip muscles in climbing stairs and rising from chairs. Symptoms began six months after the menopause, and were accompanied by episodes of unpredictable falls. She was placed upon wheat germ oil two years after the onset of symptoms, with marked improvement, maintained for three years, followed by recurrence of symptoms. In 1947 periodic joint pains led to investigation and to the diagnosis of mild gout. Upon admission, the patient could no longer mount or descend steps without support, and she walked only with a cane.

Examination showed maximal weakness in the glutei, the iliopsoas, and the quadriceps muscles. The deltoid, supraspinati, and infraspinati showed some weakness as well. Distal muscle power was well preserved. She had a more marked creatinuria than the first patient cited, but still not equal to that in the juvenile dystrophies. For two days without treatment the creatine values were:—

Volume (ml.)	Specific Gravity	Creatinine (g./24 hrs.)	Creatine (g./24 hrs.)
1100	1·018	0·644	0·332
1360	1·018	0·608	0·254

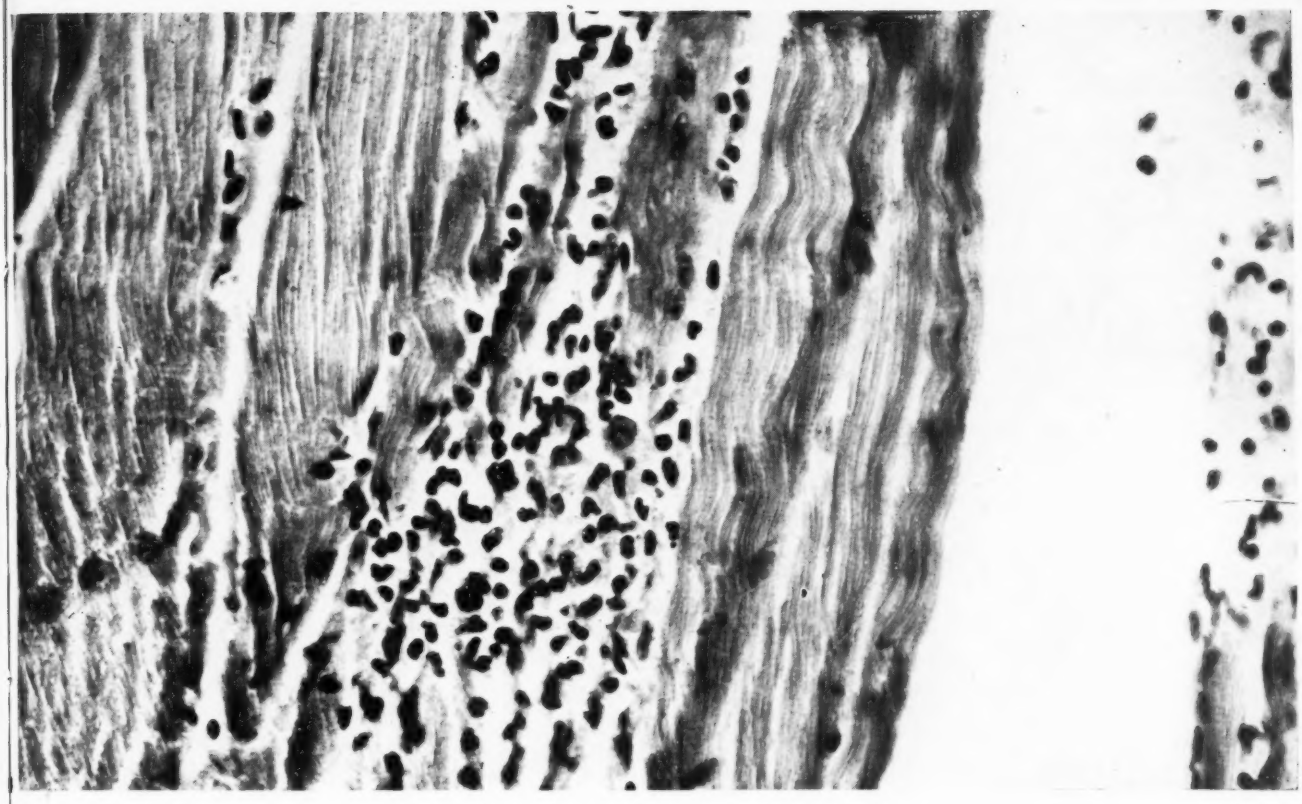

FIG. 4 (× 240).—A typical large necrotic area in patient R. P. (Case No. 1). Note interstitial space free of cells. There was rapid and dramatic improvement with cortisone.

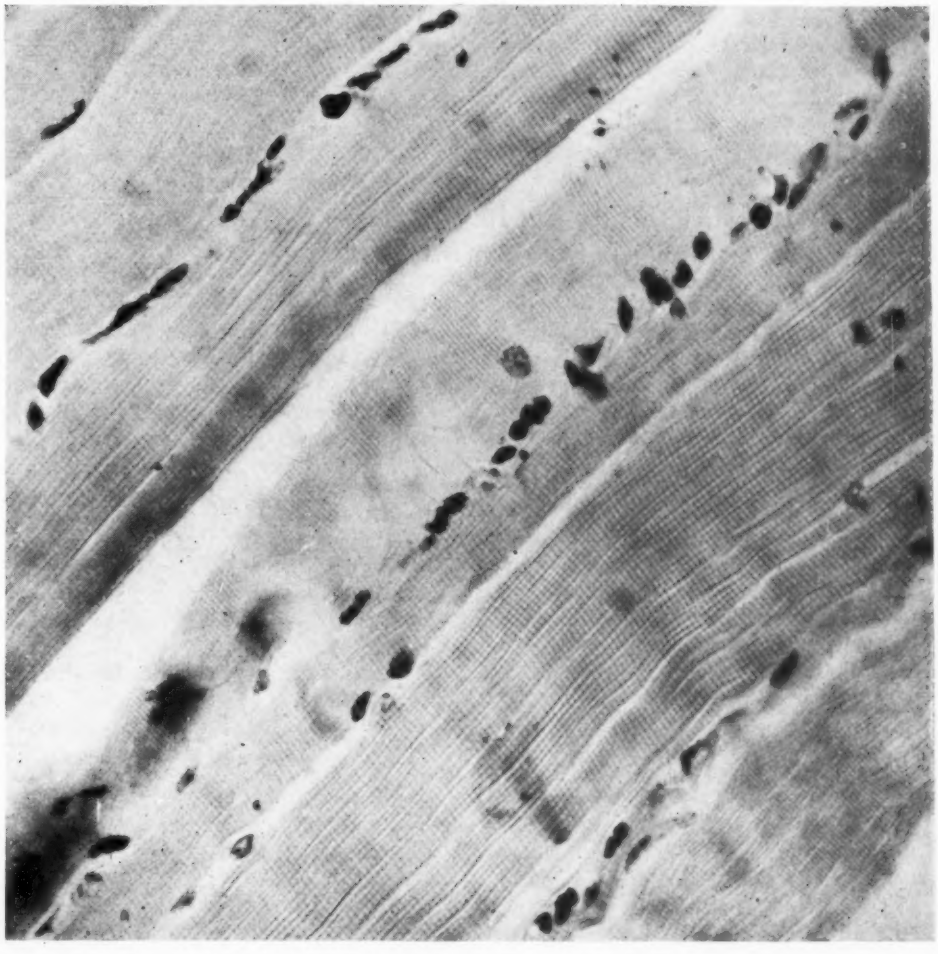

FIG. 5 (× 240).—This illustrates very early degenerative changes. The section is from the quadriceps of R. McG., the only male in this series.

A rapid increase of muscle power was noted by the fifth therapeutic day. The pains associated with the gout also markedly improved. Unlike other cases, this patient has required large maintenance doses of cortisone, up to 200 mg. every other day, to maintain improvement. Due to exogenous fluid accumulation we have recently placed her upon ammonium chloride too.

Case 3 (R. McG., aged 58).—This patient, the only man in our series, gave a history of a rapid onset of weakness of proximal girdle musculature beginning nine months before. This involved the upper extremities, so that he had difficulty in dressing himself. He walked with a cane, could not rise from a chair unassisted, and had great difficulty in getting out of bed.

Examination showed some wasting of the calves. The iliopsoas group was so weak that he could not raise his extended leg from the bed more than five times. The greatest weakness again was in the iliopsoas, quadriceps, and glutei. The quadriceps were possibly more affected than in the other cases.

Biopsy suggested the diagnosis of early dystrophy with early necrotic degeneration. These changes were not marked, and in the estimation of most observers deviated but little from normal (Fig. 5).

This patient responded dramatically to cortisone, and at the time of discharge he could raise either extended leg from the bed 30 times without fatigue. He could also rise from a chair without assistance and could walk without a cane. He is holding improvement on 200 mg. of cortisone a week—the smallest maintenance dosage we have been able to use so far.

Case 4 (S. R., aged 68).—This elderly lady noticed isolated episodes of unpredictable falling some four or five years before admission. This was followed within a year by difficulty in climbing stairs and getting out of chairs and in combing her hair. More recently, over the past nine months, she had noticed increasing weakness in her hands and legs.

Examination showed this patient to be the most severely affected of the series. Movements of the iliopsoas and glutei were not possible against gravity. There was, in addition, weakness of the triceps and the supraspinatus, the infraspinatus and the deltoid groups. The quadriceps were also severely affected but could maintain the limbs against gravity. This patient also showed moderate weakness of the extensors and flexors of the wrists.

Biopsy revealed a great amount of fat and fibrous tissue replacement of muscle fibres. Some normal muscle fibres, however, were still present, and they were of normal calibre. One necrotic area was found with an apparent phagocytic response.

In spite of the far advanced state, this patient responded well to cortisone, though not to the same degree as did the others. She could not rise from a chair, even with the aid of her arms, before therapy, but she did so readily at the close of treatment. Other muscle power improved correspondingly. Moderate contractures of the calf muscles and achilles tendons softened somewhat during treatment. She is now on maintenance therapy.

Case 5 (L. B., aged 56).—This patient had noticed weakness of the shoulder and hip muscles for two years. She stated that she could not elevate her arms above the horizontal, could not climb stairs or rise from low chairs, and had been subject to frequent falls.

Examination revealed the characteristic weakness of the proximal muscle groups, but there was also some shoulder arthropathy with limitation of abduction of the arms to 90°. Primary weakness was in the iliopsoas, the glutei, and the quadriceps. There was minimal involvement of the deltoids and supraspinati.

This patient responded rapidly to cortisone therapy. Interestingly enough, she showed the most rapid decline of all patients when on cholesterol control, and was as bad as ever by the seventh control day. She could be made to improve and relapse by alternating the regime of cortisone or cholesterol without her knowledge.

Discussion

Among the myopathies of late onset there is a group that can be distinguished both clinically and pathologically from the others. This condition is quite common. It may be wrongly laid to the general enfeeblement of age, especially since muscular wasting is seldom evident. It is characterized by weakness of the proximal muscles of the hip and shoulder girdles. It is manifested by difficulty in rising from recumbent or sitting positions or in climbing stairs and by a tendency to unpredictable falls.

The pathological process is different from that of juvenile muscular dystrophy. In the juvenile form the muscular dystrophy is that of degeneration by reduction in size of isolated muscle fibres surrounded by essentially normal fibres. The myopathy we are discussing has, in addition, a degeneration of isolated fibres which are undergoing necrotic changes. There is a dissolution of the sarcolemmal sheath, aggregation of the sarcoplasm, loss of cross striation, and an apparent clustering of the sarcolemmal nuclei. This apparently calls forth, in addition, an apparent phagocytic response. There is minimal interstitial infiltration of wandering histiocytes. This is similar to the picture described by Pappenheimer and others in vitamin E-deficient animals which could be protected by tocopherols. Some of our cases were aided by wheat germ oil. Because of this fact, and also because such dystrophic processes occur at the time of endocrine disturbance (menopause), these patients were placed upon cortisone, with the dramatic results noted above. The best guide to diagnosis appears to be in muscle biopsy, but all patients showing this clinical picture should be given a trial of cortisone therapy.

The term " menopausal muscular dystrophy " is debatable, since there is no proof of gonadal dysfunction. It is, however, the best term we can think of at the moment.

Summary

A myopathy affecting proximal girdle muscles (hips and shoulders) can be distinguished from other myopathies of late onset by a typical pathological picture. This condition occurs in the post-climacteric period. In this series it was found predominantly in the female.

The necessity of biopsy for diagnosis is emphasized.

Some of these patients have been treated over long periods of time with wheat germ oil, with temporary relief for periods up to three years.

The similarity of the pathological changes to those described in vitamin E-deficient animals is discussed.

These patients have responded well to administration of cortisone acetate. Maintenance dosage is necessary.

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THE SURGICAL TREATMENT OF EXTRAPYRAMIDAL DISEASES*

BY

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Strictly speaking there is no satisfactory surgical treatment of any of the disorders which arise from involvement of the extrapyramidal systems. Diseases which involve the extrapyramidal components of the central nervous system are numerous and give rise to many different clinical manifestations. Only a very small minority of the victims of these diseases present problems which can in any measure be solved by surgical therapy. And even in such cases surgical measures are, at least at this moment, never curative and seldom benefit more than one of the many symptoms which are present. Even in those few cases surgical treatment usually consists of substituting an undesirable neurological deficit for an even more disabling and disturbing manifestation of the disease. There are now reasons to hope that this may not continue to be true in the future.

With few exceptions the disorders arising from lesions of the extrapyramidal systems which are so commonly seen in man are peculiar to him. Rarely has it been possible to produce in experimental animals disturbances sufficiently akin to those seen in man to permit us to make reliable investigations of these problems in the experimental laboratories. Similarly, nature has failed to provide us with animals afflicted with such diseases as those seen in man. The problem is further complicated by the fact that the central nervous mechanism which controls muscular activity in man is different in many respects from that present even in the subhuman primate, and widely different from that found in lower forms. It is thus obvious that if we are to study these diseases we must study them in man. This is not the only circumstance in which we must agree with the French philosopher, Pierre Charron, and with England's Alexander Pope that " the proper study of mankind is man ", but it is one of the most outstanding.

We have not time now to give attention to the entire question of the organization of the central nervous mechanism for the control of human muscular activity. That is a full subject in itself. However, we must tarry briefly to discuss just what is meant by the term " extra-pyramidal systems ".

A few years ago " extrapyramidal system " and " basal ganglia " were almost if not quite synonymous. As recently as 1928 in the index of the late Kinnier Wilson's book, *Modern Problems in Neurology*, we find " Extrapyramidal Syndromes. *See* Corpus striatum". And Grinker in 1934, in the first edition of his book, *Neurology*, p. 405, says :

> " Numerous large and small ganglia at the base of the brain, forming together a relatively large area of tissue, comprise the extrapyramidal motor system."

Other examples could be cited but this is sufficient to indicate the inadequate conception of the extrapyramidal systems which was so recently held. Furthermore, at that time it was commonly thought that there were few if any connexions between the cerebral cortex and the basal ganglia and that the pyramidal and extrapyramidal systems formed autonomous units which functioned nearly independently of each other, yet collaborated in the dual control of the muscular system by means of some obscure, almost ethereal coordinating mechanism. The extrapyramidal system was thought to be " not directly concerned in the production of voluntary movement " (Walshe, 1941), while the pyramidal system and the cerebral cortex were generally regarded as being in no way related to those states which were commonly classified as " extrapyramidal disorders ".

Although our knowledge of the extrapyramidal systems, their structure, functions and disorders, is still woefully incomplete, it has progressed far beyond the state of ignorance and confusion indicated above. It is now well established, as one might have anticipated in view of the beautiful, smooth coordination which characterizes all normal

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muscular activity, that the pyramidal and extrapyramidal systems, the motor cortex and the basal ganglia and other subcortical motor centres, are all closely integrated and coordinated into one mechanism which is concerned with the control of muscular activity. The overall control of this neural mechanism is exercised through the precentral motor cortex. The extrapyramidal system is not an independent neural mechanism ; neither is it a single unitary system. The extrapyramidal systems consist of a group of complex neural organizations, all of which stem directly from the precentral motor cortex.* Areas 24, 8, 2, and 19 also project to the caudate nucleus and probably must be considered as part of the extrapyramidal systems having a functional activity akin to that of the connexions known to exist between area 4s and the caudate nucleus. In all probability all of the anatomical extrapyramidal connexions between the precentral motor cortex and the subcortical centres are not known ; certainly many details regarding them are still a mystery, and without a doubt the functional activity of many of these connexions is still to be learned. At the present time it is known that there are descending connexions from area 4s of the precentral motor cortex (and also from areas 24, 8, 2, and 19) to the caudate nucleus ; from areas 4 and 6 to the putamen ; from area 6 to the external segment of the globus pallidus ; from the precentral motor cortex (areas 4, 4s, and 6) to the zona incerta, the red nucleus, the substantia nigra, and the reticular formation of the mesencephalon and pons. There is also a large group of descending fibres which pass from areas 4 and 6 to the pontine nuclei. Here the impulses are relayed via the middle cerebellar peduncle to the cortex of the neocerebellum, primarily in the cerebellar hemispheres. There is also a very heavy efferent projection from the precentral motor cortex to the lateral nuclear mass of the thalamus, but it might be reasonably argued whether these cortico-thalamic connexions are directly concerned in the control of muscular activity and should therefore be classified as extrapyramidal. I would define the extrapyramidal systems as those complex groups of descending fibre systems which are directly concerned with the control of muscular activity, which arise in the cerebral cortex and descend through various subcortical centres through a variable number of synapses but have no fibres which pass directly from the cerebral cortex to the spinal cord.

The study of the functional activity of the extrapyramidal systems is very largely dependent upon information which it has been possible to accumulate from the study of laboratory animals, particularly the subhuman primates, such as the monkey, the baboon, and the chimpanzee. How completely this information is applicable to the human nervous system is uncertain and must be inferred from inadequate observations. Even in the experimental animals, however, our knowledge of these functions is distinctly imperfect, particularly as concerns the correlation of structure and function. Although we know of a rather wide variety of extrapyramidal mechanisms there are still many situations in which we do not know which function a given system is responsible for, or when the function is known, we are often unfamiliar with the structural means by which it operates.

The various *known* functions of the extrapyramidal systems can be classified as follows : (1) the production of integrated primary movements of the skeletal musculature ; (2) the integration of associated and ancillary movements ; (3) the control and inhibition of postural reflexes ; (4) the suppression of electrical activity in other areas of the cortex ; (5) the imperfect and partial control of visceral and vegetative functions and their integration with the activity of the skeletal musculature.

The movements produced by the extrapyramidal systems are crude and coarse. They lack the fine, discrete, precise nature characteristic of movements produced by the pyramidal system. They are nonetheless voluntary and purposeful. The movements produced by the extrapyramidal systems tend to involve the proximal joints such as the shoulder and elbow, hip and knee, in contrast to the movements produced by the pyramidal tract which are most extensive in the digits. There is no evidence available at this time as to which of the various extrapyramidal systems is concerned in this production of voluntary movements.

Fibres from the precentral motor cortex to the basal ganglia, to the brain stem, and to the pontine nuclei where impulses are relayed on to the cerebellum appear to be concerned in the innervation of associated and ancillary movements which, although not directly concerned in the principal or primary movement, are nevertheless of great importance in the smooth, well coordinated performance of the act. The role which each one of these extrapyramidal systems plays in the integration and production of these associated movements is not clearly understood.

One of the most important functions of the extrapyramidal systems is the control of the postural reflexes. Such reflexes are obviously extremely

* For the details and bibliography of the anatomical and physiological facts stated here see " The Precentral Motor Cortex " edited by Bucy (1949).

important in the physical economy of the organism, but unless properly controlled and their actions appropriately coordinated with voluntary muscular activity, they would greatly interfere with such activity. It is likely that different parts of the extrapyramidal systems are concerned with the inhibition and control of these various reflexes. It has been shown, however, that the strip 4s, which lies between 4 and 6 in the monkey and between area 4a and 6 in man, is probably the most important of the cortical areas so concerned. Although this strip has several descending projections, the one which is particularly concerned with the control of the postural reflexes is that which descends from area 4s through the internal capsule and cerebral peduncle to terminate in the reticular formation in the upper bulb (Magoun and Rhines, 1946). From here the inhibitory impulses are relayed on to the spinal cord via a reticulo-spinal tract which appears to be concentrated in, although not confined to, the ventral part of the lateral funiculus of the spinal cord. Although this neural mechanism is primarily concerned in the control of the postural reflexes, it is noteworthy that, at least under experimental conditions, it is capable of inhibiting all types of motor activity. Thus experimental stimulation of this system at the cortical level can arrest the clonic after-discharge produced by intensive stimulation of area 4 in the precentral motor cortex ; it can inhibit spontaneous muscular activity in the extremities ; it can abolish the spasticity commonly associated with light ether anaesthesia ; and stimulation of the bulbar reticular formation can hold completely in abeyance movements which would be otherwise elicited by the electrical stimulation of area 4. It is not to be presumed, however, that this area 4s-reticulo-spinal system is the only extrapyramidal mechanism which is concerned in the control of postural reflexes, although it does seem to be the principal and most important system so concerned. There is definite evidence that the spasticity which develops following the removal of all of the precentral motor cortex is greater than that which develops after the destruction of area 4s alone. Furthermore, the spasticity which appears after an extensive cortical lesion of the precentral motor cortex in man is not as intense as that which commonly develops after a severe lesion of the internal capsule. Lesions still farther " caudalward ", in the mesencephalon, are not commonly available for study in man but the spasticity which appears in such cases is intense and probably more intense than that associated with capsular lesions. In addition, there is definite evidence that stimulation of the anterior lobe of the cerebellum is capable of inhibiting postural reflexes and that destruction of this part of the cerebellum leads to the appearance of a generalized spasticity which is akin to decerebrate rigidity. It thus seems obvious that controlling impulses descend from the cortex to the basal ganglia as well as to the reticular formation and that in these various subcortical ganglia they are elaborated and enhanced by influences from the basal ganglia, the brain stem, and the cerebellum, thus augmenting the inhibitory effect as it descends from the precentral motor cortex toward the spinal cord.

Area 4s (like areas 8, 2, 24, and 19) is also capable of inhibiting the electrical activity of other areas of the cerebral cortex. This effect is mediated through the caudate nucleus and thus follows an entirely different pathway from the impulses which are concerned in the control of postural reflexes and the inhibition of other peripheral motor responses. Whether this effect of inhibiting other areas of the cerebral cortex is directly or remotely concerned in the control of peripheral muscular activity and should, therefore, be classified, under our definition, with the other extrapyramidal activities cannot be stated at this time.

The least complete control which the precentral motor cortex exercises is over the various vegetative and visceral functions of the body. This is probably the least well understood of the various functions of this portion of the brain. There can, however, be little doubt that such control exists. It is concerned with gastrointestinal, vasomotor and cardiac activity, piloerection, and the secretion of perspiration. There is reason to believe that, although many of these functions are executed over unknown extrapyramidal pathways, the pyramidal tracts may also be concerned in some of them, notably vasomotor activities. Furthermore, there is good evidence that other parts of the cerebral cortex lying near but not in the precentral motor cortex are concerned with still other activities of this general category. Thus the frontal eye fields (principally area 8) which lie immediately anterior to area 6 are concerned with control of the pupils. Some structure in or near the spatially closely related orbital surface of the frontal lobe, uncus of the temporal lobe and anterior portion of the Island of Reil, is concerned with the control of respiration, gastrointestinal activity, and vasomotor phenomena. The importance of the control of these visceral and vegetative functions in connexion with the activity of the skeletal muscular system is obvious and there can be little doubt that such control, limited and imperfect as it is, resides in the precentral motor cortex in order to control these functions in the best interests of the total economy of the organism.

Extrapyramidal Disorders

Those disturbances which we have come to designate as " extrapyramidal " are so classified because they arise as the result of pathological lesions located somewhere within these extrapyramidal systems. Thus parkinsonism or paralysis agitans (and thus the tremor at rest which is so commonly a part of this syndrome) is associated with lesions in the substantia nigra or the globus pallidus, or often in both. Action or intention tremor, on the other hand, develops in association with lesions which destroy the dentato–rubro-thalamic system. Choreo-athetosis usually appears following a lesion of the striatum (caudate nucleus and putamen) or of the anterior half of the lateral nucleus of the thalamus. Huntington's chorea is associated with severe atrophy of the lenticular nucleus (globus pallidus and putamen), but the lesion responsible for the development of the abnormal and involuntary movements which are characteristic of Sydenham's chorea have never been accurately defined. Hemiballismus, or hemichorea as it is sometimes called, appears following severe damage to the subthalamic nucleus of Luys.

Although some of the disorders which have been listed here are associated with true neurological defects, such as the absence of associated and expressive movements in Parkinson's syndrome, we are primarily concerned here with the positive neurological abnormalities which appear in these conditions and in association with these lesions. This is one of the clearest illustrations of the dictum of Hughlings Jackson (1931) that whereas destructive lesions of the nervous system may produce neurological deficits or negative manifestations, they cannot directly produce positive phenomena. Such destructive lesions only permit positive manifestations, such as involuntary movements, to appear as the result of the release of other and intact structures to abnormal activity. For years the location of the pathological abnormality focused all attention upon the basal ganglia and intensive but futile search was made here for the neural mechanism responsible for the abnormal involuntary movements which characterize these " extrapyramidal diseases ".

There had been several minor indications from time to time that the mechanism responsible for these abnormal movements was connected with the downward projection from the precentral region. Parkinson in his original description in 1817 had pointed out that the tremor of the shaking palsy disappeared if the patient developed a hemiplegia as the result of a capsular lesion, and Jakob (1923) had described a case of athetosis in which the abnormal movements disappeared when the patient became hemiplegic. Horsley, in 1909, and others had presented even more definite evidence of such a relationship when they showed that destruction or removal of the precentral gyrus would abolish the abnormal involuntary movements of athetosis. In the main, however, these observations attracted little attention. In 1925 and 1928 the late Kinnier Wilson postulated that the abnormal involuntary movements characteristic of choreo-athetosis were produced by impulses travelling over the pyramidal tract from the precentral region, and that this system had been released to such abnormal activity by the destructive lesions in the subcortical centres, particularly the " cerebello-subthalmic-cortical " afferent pathways. Although we would modify and elaborate some of Kinnier Wilson's ideas in some respects, the clinical observations of the past 20 years have, in general, substantiated his hypotheses.

In 1931 a 7-year-old girl with unilateral choreo-athetosis (and unilateral convulsive seizures) was operated upon and a considerable portion of the " arm " area of the precentral gyrus extirpated (Bucy and Buchanan, 1932). Following the operation she had no choreo-athetoid movements and in the ensuing years these movements have never returned. Subsequently other patients suffering from choreo-athetosis have been similarly operated upon and other surgeons have reported other successful cases of a like nature.* From these observations it has gradually become apparent that for the most satisfactory results in the relief of choreo-athetoid movements it is necessary to remove all of the representation of the affected extremity in the precentral gyrus, i.e., area 4, and the neighbouring parts of the first and second frontal convolutions, i.e., area 6. As has been pointed out earlier, areas 4 and 6 of the precentral motor cortex give rise to both pyramidal and extrapyramidal fibres and it would not be possible from the evidence thus far cited to determine which of these fibre systems is concerned in the production of these involuntary movements. However, Putnam (1938 a and b) and others later demonstrated that division of the anterior column of the spinal cord likewise will often greatly reduce the intensity of these movements. As such an operation would

* Occasional cases have been reported in which removal of the " premotor " area has not affected the abnormal involuntary movements of choreo-athetosis. In practically every instance it has been clear that the representation of the involved extremities in areas 4 and 6, as described above, has not been removed. Incomplete extirpations or inaccurately placed ablations only lead to unsatisfactory results but do not contradict the statements which have been made here. In the case published by Davison and Goodhart (1938) and again by Davison (Case 14, 1944) it is obvious that the extirpation was in the inferior part of the frontal lobe, well anterior to the precentral gyrus and did not encompass the representation of the right arm and leg which were involved by the involuntary movements.

divide many extrapyramidal fibres while leaving the lateral pyramidal tract intact, it is reasonable to conclude that it is the extrapyramidal and not the pyramidal fibres which are primarily concerned in mediating the nervous impulses which give rise to the abnormal involuntary movements of choreo-athetosis.

Unfortunately, the operation of anterior cordotomy has not proved highly satisfactory in the treatment of these conditions. This is most regrettable as whereas the cortical operation of necessity destroys pyramidal as well as extra-pyramidal fibres and thus results in a severe degree of paralysis, the anterior cordotomy would spare the pyramidal tract and thus interfere much less with voluntary muscular activity. However, whereas the cortical procedure, when properly performed, is capable of completely and permanently abolishing the abnormal involuntary movements of choreo-athetosis, the anterior cordotomy rarely more than diminishes these movements and even when the results are the most striking, they are often not permanent. This is probably to be attributed to the fact that a division of the anterior columns of the spinal cord still leaves many of the extrapyramidal fibres intact. The following case is an example of the favourable, but temporary, results which can at times be obtained with anterior cordotomy and the contrasting more complete and permanent results which can be obtained in the same case by cortical excision.

Case Reports

Case 1.—E.M.S., a woman 26 years of age, was referred by Dr. Eric Oldberg, of Chicago. At the age of 2½ years she developed abnormal involuntary movements of her left arm and leg for no known reason. The movements gradually grew more severe, and, by 1936, when she was 23 years old, they had become so severe that she was confined to a wheel chair into which she had to be tied to prevent her being thrown out by the violent involuntary movements. On July 1, 1936, Dr. Oldberg crushed the anterior column of the spinal cord on the left side at the level of the second cervical anterior root. "Following the operation all the abnormal movements stopped immediately except for a slight, almost imperceptible, jerking of the left shoulder girdle." Unfortunately such a complete abolition of the abnormal movements did not persist. By September the patient wrote that the jerking had returned but was not as severe as before the operation. Thereafter the involuntary movements of the left arm and leg gradually increased in severity, although they never returned to their former degree of violence.

On July 14, 1939, she was admitted under my care to the University of Chicago Clinics. There were occasional involuntary twitchings of the left side of the face. The left arm made continuous purposeless writhing, twisting movements which involved all joints—the shoulder, elbow, wrist, and fingers. There were less severe movements of the left ankle and great toe. These involuntary movements were constantly present when she was awake and ceased only during sleep. She was still confined to a wheel chair but no longer had to be tied in.

On July 27, 1939, the right precentral motor cortex was exposed at operation and that portion of it removed from which movements could be elicited in the left upper and lower extremities by electrical stimulation (Fig. 1). The extirpation also included the paracentral lobule on the medial surface of the hemisphere and the most posterior part of the first frontal convolution. However, the inexcitable portion of the precentral gyrus lying between the last point from which movements of the fingers could be elicited and the representation of the face was not removed. This, as we shall see, was a mistake.

On the seventh postoperative day slight involuntary movement of the left fingers was noted. On the twenty-fourth postoperative day involuntary rotation of the left forearm was seen. Thereafter such movements were seen only rarely until the 90th day, when involuntary movements of the left wrist and fingers were obvious and persistent. These continued but otherwise the involun-

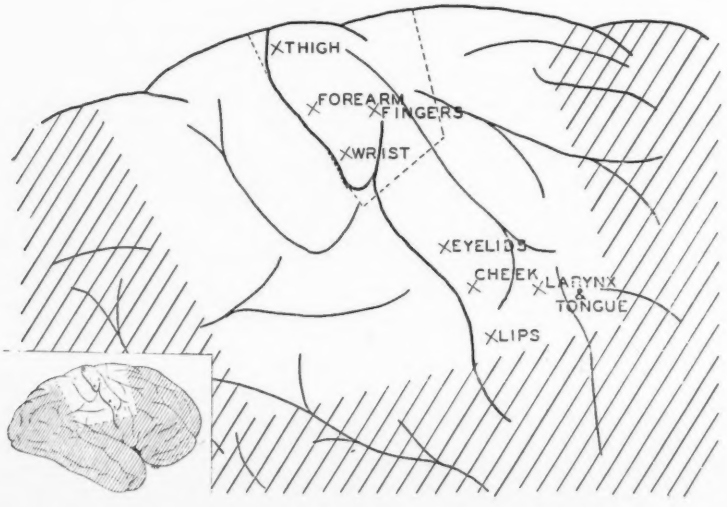

FIG. 1.—Sketch of the cerebral cortex (Case 1) exposed at the first operation on July 27, 1939. The points from which movements of various parts were elicited by electrical stimulation are marked by crosses. The area extirpated is outlined by broken lines.

tary movements which had been so continuous and severe before the cortical extirpation did not return. It was decided that the inexcitable portion of the precentral motor cortex lying ventral to the ablation was responsible for these movements. However, as they were not severe nothing was done about them until the patient returned asking that a further cortical extirpation be made. This was done on January 26, 1943. The former osteoplastic flap was again reflected. On electrical stimulation of the precentral gyrus just ventral to the scar of the previous extirpation, movements of the left forearm and hand were produced. Further ventrally electrical stimulation elicited movements of the left eyelids, and below that point movements of the left side of the face and of the left platysma myoides. The precentral gyrus was extirpated from just above the point at which movements of the left side of the face were produced (Fig. 2). In other words, that portion of cortex from which movements of the left upper extremity and of the left eyelids were produced was extirpated. This was largely the portion of the precentral gyrus which was inexcitable at the first operation. In addition, the scarred base of the cavity left by the former operation was also removed. The cavity left after this second operation measured 6 cm. long, 1·4 cm. wide and 2 cm. in depth.

The patient has continued to return for examination at frequent intervals. She is active and does most of the housework in the home of her parents where she lives. She also does beautiful needlework, although she is only able to use the left hand to hold the embroidery hoops. The left upper extremity is otherwise of very limited usefulness. The usefulness of the left lower extremity has been enhanced by an operation on the peripheral nerves to the leg and an arthrodesis of the ankle joint and she walks well although with a definite limp. The involuntary movements have not returned some seven years after the last operation. She is one of our most appreciative patients and has been restored from a life of inactive wheel chair existence to one of comparative usefulness.

Different operations for the relief of the abnormal involuntary movements of choreo-athetosis have been performed by other surgeons. Extirpation of the frontal lobe immediately anterior to the excitable cortex of the precentral motor cortex have been made. Most of the operations of this type have been performed by Klemme (1940), and unfortunately the details as to the patients, their illness and symptomatology, the operations and the results obtained have never been published. Most other surgeons (Sachs, 1942; Putnam, 1933; and others) have not been able to obtain the fortunate results which Klemme has indicated have followed such a procedure.

Although Wilson believed that the involuntary movements of choreo-athetosis were produced by impulses travelling over the descending fibres from the precentral region he did not believe that tremor was similarly produced. However, there were other evidences that it was. As previously noted, Parkinson and later others, had noted that the tremor of paralysis agitans was abolished when apoplexy paralyzed the involved extremities. More recently Aring and Fulton (1936) showed that the intention tremor produced by cerebellar lesions could be abolished by removal of areas 4 and 6 in the monkey. With these observations to guide us, on October 12, 1937, the representation of the upper extremity was removed from the left cerebral hemisphere of a man who suffered from both tremor-at-rest and intention tremor as the result of a severe cranio-cerebral injury (Bucy and Case, 1939). This operation was followed by a complete cessation of the tremor and the tremor had not returned when the man was last heard from several years later. In the years which have followed a few other patients with tremor have been seen who were thought suitable for such an operation. Several of these have been operated upon. It is now obvious that tremor, whether at rest or of the intention variety, can be completely abolished by the extirpation of the area of representation of the involved

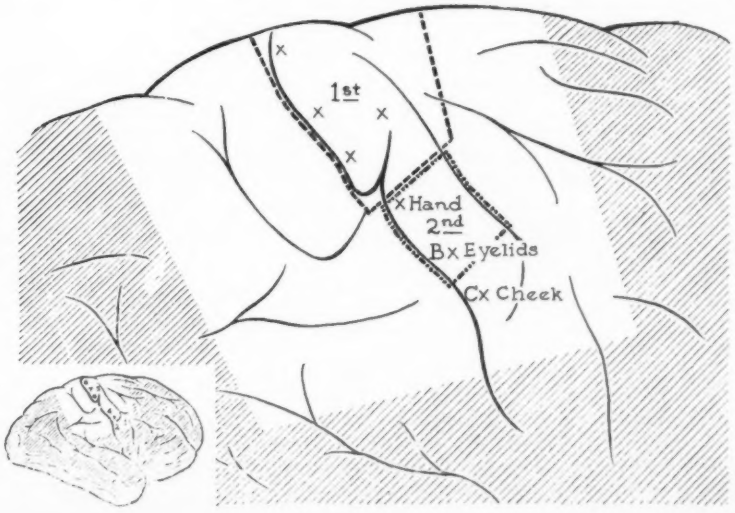

FIG. 2.—Sketch of the cerebral cortex (Case 1) exposed at the second operation on January 26, 1943. The site of the first extirpation is outlined and designated "1st". The points from which electrical stimulation provoked movement of the left hand, left eyelids and left cheek at this second operation are marked; those for the eyelids (Bx) and cheek (Cx) correspond to those demonstrated in 1939. The "hand" focus found on this occasion was demonstrated for the first time. The second extirpation is outlined and designated "2nd".

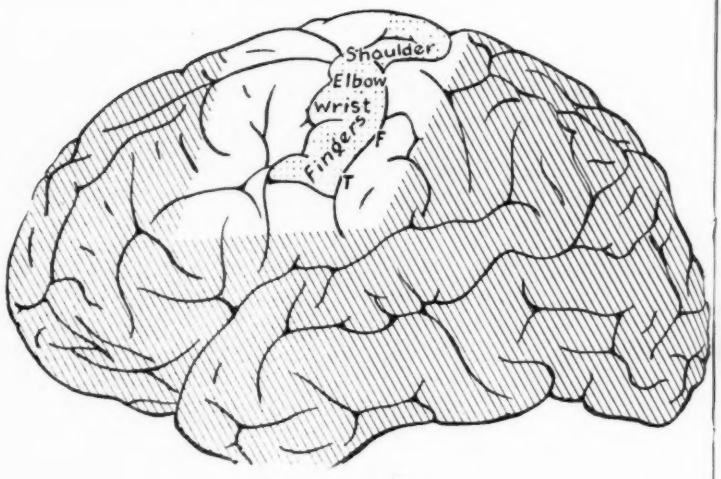

FIG. 3.—Sketch of the cerebral cortex (Case 2) exposed at the operation on October 22, 1947. The responses to electrical stimulation of the surface of the precentral gyrus are indicated by names of the part involved. The area extirpated is stippled. "T" indicated the approximate location of the point on the anterior surface of the postcentral gyrus deep in the central fissure, stimulation of which, after extirpation of the precentral gyrus, elicited movement of the right thumb, while the point "F", similarly situated, was associated with movement of the right index finger.

extremity (or extremities) in the precentral gyrus alone, i.e., area 4. At one time it was hoped that removal of only the posterior half of the precentral gyrus (area 4γ which contains the Betz cells) would suffice permanently to abolish such tremor. However, such a limited extirpation proved inadequate and the tremor returned in a mild form.

That the effect of the removal of the precentral motor cortex is a precise one dependent upon the destruction of specific cells and fibres related to the affected part is clearly shown by the following case.

Case 2.—G.B., a 28-year-old woman, was referred by Dr. Adrien Verbrugghen of Chicago. She had been well until January 12, 1941, when she fell from a moving automobile and struck her head on the concrete pavement. She was unconscious for the next 14 weeks. Subsequently exploratory trephination and later an exploratory osteoplastic craniotomy failed to disclose any haematoma. When the patient recovered consciousness she had an aphasia, dysphagia, a severe incoordination of the movements of the extremities, and a right hemiplegia. Her condition gradually improved but she never became able to walk. About nine months after the injury tremor appeared in the right upper extremity. It gradually increased in severity and spread to the right lower extremity. In September, 1947, a pneumoencephalogram demonstrated an increase in the size of the subarachnoid spaces over the cerebral hemispheres and a dilatation of the ventricular system.

She was admitted to the Illinois Neuropsychiatric Institute on October 2, 1947. The most striking abnormality was a severe tremor which was greatest in the right hand and arm but was also present in the right lower extremity. This tremor was present with the extremities at rest and was often so severe that the hand flapped against the side of the body unless the patient held it with the left hand. However, the tremor was much more severe whenever voluntary movements were attempted with the right extremities. There was marked limitation of voluntary movements in the right extremities and, as noted above, she was unable to walk except with a great deal of assistance, and then did so very poorly. The right upper extremity was held in a flexed position and was moderately spastic. The forearm was pronated. All tendon reflexes were hyperactive; those on the right were more active. Babinski's sign was present bilaterally, but was more easily elicited on the right side. The abdominal reflexes were present and equal. Cutaneous sensibility (touch, pain, heat, and cold) was slightly diminished on the entire right side. There was an astereognosis in the right hand and she was unable to recognize figures written in the right palm. Her speech was quite limited and difficult. She spoke slowly and very jerkily. Her pronunciation was poor. There was a complete paralysis of the external rectus muscle of the left eye, the right pupil was slightly larger than the left, both reacted to light but there was no reaction of accommodation and she could not converge her eyes. There was a slight drooping of the right side of the face.

It was felt that this young woman had sustained a severe injury to the upper pons and midbrain, particularly on the left side, with an involvement of the left abducens nucleus, the left cerebral peduncle and the dentato-rubro-thalamic tract after it had crossed from the right superior cerebellar peduncle to the left side of the midbrain, a condition similar to that so well described by Kremer, Russell, and Smyth (1947). It was decided to remove the representation of the upper and lower extremities from the left precentral gyrus in the hopes of abolishing the tremor.

On October 22, 1947, under ether anaesthesia the left precentral region was exposed. With electrical stimulation (60 pulses per second, 2 sigma falling phase and various voltages up to 20) movements of the right thumb, fingers, wrist, elbow, and shoulder were elicited. No movements of the lower extremity were produced. The representation of the right upper extremity in the precentral gyrus and the gyrus up to the midline were removed (Fig. 3). The "face" area was carefully preserved to avoid interfering further with the patient's already greatly disturbed speech. After the block of precentral gyrus had been cleanly and completely removed the exposed anterior surface of the postcentral gyrus which had been buried in the central fissure was stimulated. Stimulation of the more ventral part with a current of low voltage elicited flexion of the thumb; stimulation with a stronger current (12 volts) produced lateral deviation of the index finger and from a point located nearer the midline supination of the wrist.

On recovery from the operation there was no trace of the tremor. The right extremities were flaccid and completely paralyzed. Sensation was unchanged, but for a time her speech was worse because of the addition of some aphasic difficulties. This, fortunately, was quite temporary. Soon voluntary movement returned to the right hip and the entire lower extremity progressively became stronger. About six weeks after the operation voluntary movement first appeared in the right arm, but practically no voluntary movement ever returned to the fingers, hand, or wrist. At this same time a fine tremor returned to the right thumb. This gradually increased until a definite tremor-at-rest was constantly present in the thumb. This has continued ever since without much material change. There has also been some tremor of the right hand and wrist which is present only on movement of the right upper extremity. Her condition remained stationary and was the same when she was last seen, 14 months after the operation.

In my experience tremor, either at rest or in association with voluntary movement, has been abolished only when the representation of the affected extremity has been destroyed in the precentral gyrus. Sachs (1942) has noted that removal of the cortical tissue immediately anterior to the precentral gyrus, i.e., area 6, is not effective in relieving tremor. As a major part of the pyramidal tract arises from the precentral gyrus (area 4) while none is known to arise from area 6, this strongly suggests that tremor is mediated by impulses which descend via the pyramidal rather than the extrapyramidal fibres. However, this evidence is not conclusive as extrapyramidal fibres arise from both areas 4 and 6 and might be the ones concerned. Valuable additional evidence on this point is presented by the operations on the spinal cord in cases of tremor. Both Oldberg (1938) and Putnam (1938b) failed to affect the tremor of paralysis agitans by destruction of the anterior column of the spinal cord—a procedure which had had a very definite ameliorating effect in cases of choreo-athetosis. This would indicate that if tremor is produced by impulses travelling by way of the extrapyramidal systems the fibres involved must be different ones from those concerned in producing choreo-athetosis. Putnam (1940), and others who have followed his lead (Oliver, 1949 ; Ebin, 1949) have demonstrated that division of the lateral pyramidal tract in the spinal cord effectively reduces the tremor of parkinsonism. Thus it would seem quite conclusive that interruption of the pyramidal tract is essential to the abolition of tremor-at-rest except for some other observations which are as yet imperfectly understood. Browder (1948) has operated upon a considerable number of patients with paralysis agitans by dividing the anterior limb of the internal capsule. The tremor has been markedly reduced in most cases without the production of any considerable hemiparesis. According to Levin's (1936 and 1944) studies the fibres in the anterior limb of the internal capsule are connected with that portion of the frontal lobe anterior to the motor eye field (area 8) or what has been termed the prefrontal or frontal association areas. So far as is known all of the projection fibres of areas 4 and 6 pass downward in the *posterior* limb of the internal capsule.

Furthermore, there is no evidence that destruction of the cortex of the frontal lobe anterior to area 8 has any effect on tremor.* One cannot, therefore, be other than puzzled by Browder's (1948) observations. There are, however, two facts which are important in this connexion and which must not be lost sight of. To date there have been no published reports of postoperative examinations of the brains of any patients who have been operated upon in this fashion and in whom the tremor has been abolished. Furthermore, the division of the internal capsule, which is conducted under local anaesthesia, is continued posteriorly until there is a demonstrable " marked paresis " of the contralateral upper and lower extremities, and postoperatively there is a variable, though usually mild, interference with voluntary control of the upper extremity and the patient often walks with a slight limp. These facts would indicate that the exact nature and extent of the operative procedure on the internal capsule is as yet unknown. Browder feels that this operation should not be performed bilaterally because of undesirable effects.

Recently Walker (1949) and White (1950) have both reported a favourable effect upon parkinsonian tremor from section of the lateral segment of the cerebral peduncle. Walker has operated upon five patients in this manner and at least two have had considerable hemiparesis postoperatively. In White's single case there was no hemiparesis. Presumably the pyramidal tract was damaged little if at all in the more successful of these operations. Obviously, in Browder's operation the fronto-pontine tracts would suffer the greatest damage. (In the cerebral peduncle these pathways occupy the medial segment.) In Walker's and White's operations the parieto-pontine (temporo-pontine) fibres would be the ones divided.

* In this connexion I have observed one patient with a typical parkinsonian tremor-at-rest and a severe behavioural disturbance as the result of encephalitis. Because of the severity of the disturbance of behaviour a bilateral frontal lobotomy was performed on January 19, 1948, by a transection under direct vision of practically the entire white matter of both frontal lobes in the plane of the coronal suture. The effect upon the patient's behaviour has been most gratifying and permanent. Quite unexpectedly the tremor was in complete abeyance immediately after the operation. This continued for some time and then the tremor gradually began to reappear and within three months after the operation it was the same as it had been previously.

Naturally these plus our own observations on the effects of extirpation of the precentral gyrus create not a little confusion as to just which pathway is primarily concerned in the production of tremor-at-rest. Solution of this problem will, obviously, have to await further studies. In the meantime, however, the work of both Browder and Walker gives reason to hope that it may be possible eventually to abolish the tremor of parkinsonism without paralyzing the affected extremities.

Thus far we have stressed the effect of properly performed extirpations of the precentral motor cortex upon the abnormal involuntary movements of disorders of the extrapyramidal systems. It is equally important that we stress that all clinical investigations on this problem are still experimental, that the related problems are by no means solved, and that but few patients present a condition which is suitable for treatment in this manner. Cases of choreo-athetosis are suitable for cortical excision only when (1) the involuntary movements are sufficiently severe to be incapacitating either to the involved extremity or to the individual as a whole; (2) the involuntary movements are sufficiently severe so that both the patient and the physician agree that it would be worthwhile to take the usual risks of a craniotomy, with the possibility that convulsive seizures may follow the operation (present in about 10% of the cases and usually easily relieved by anti-convulsant drugs), and that the hemiparesis which is usually already present in these cases may be somewhat increased; (3) the involuntary movements are limited to one or both extremities on one side of the body.

The same qualifications apply to the selection of patients with tremor for operation. But in addition it must be further borne in mind that the operation will not favourably affect such other manifestations of the disease as the rigidity, the slowness of movement, the mask-like facies, the stooped posture and abnormal gait, the loss of associated movements and poverty of all movement, and the excessive salivation and the oculogyric crises which are found in many patients with tremor of the parkinsonian type. Likewise, the operation will not favourably influence the natural progress of the disease, and thus the condition in a patient with paralysis agitans limited to one arm will progress to involvement of the other extremities even though the tremor be abolished in the initially affected extremity by an operation upon the cerebral cortex. It is obvious, therefore, that abolition of the tremor of parkinsonism by removal of the appropriate part of the precentral gyrus is indicated only in those few cases where the tremor is limited to one side of the body and when the disease can be reasonably thought to have been arrested. Naturally, I have operated upon but few patients with tremor-at-rest. Those who have been operated upon have had their tremor as the result of cerebral trauma (when it is often associated with an even more violent intention tremor), or of a luetic mesencephalitis in which the syphilitic infection has been rendered inactive by antiluetic therapy. Intention tremor is more often the result of some non-progressive condition, such as cerebral trauma, and is, therefore, more often suitable for such operative relief. I have not personally had any experience with the operations upon the cerebral peduncle (Walker) or the subcortical fibres in the precentral region (Meyers, Sweeney, and Schwidde, 1950) which have been performed in cases of hemiballismus, but welcome all information regarding these and other well considered, carefully planned and executed operations which shed any light upon the problems of pathogenesis, pathological physiology, and treatment of the extrapyramidal diseases which are characterized by abnormal involuntary movements. Only by the careful accumulation of information in this fashion will these problems ultimately be solved.

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DISABILITIES AND PROGRESS IN A DYSPHASIC UNIVERSITY STUDENT

BY

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The relations between language and thought in the normal person, and the connexion between the forms of their disturbance in the dysphasic, are questions which have aroused much discussion and little conclusion. But at least it would seem clear that the nearer an individual's daily occupation approaches to the purely intellectual, the more it is likely to be impeded by even a mild degree of dysphasia. It is tempting to suppose that if an intellectual occupation were nevertheless pursued, the study of its products in the form of written material might contribute to an understanding of the relations of thought and language, at least in respect of their modes of breakdown. So uncommon is it, indeed, for any degree of dysphasia, however slight, to leave the patient still capable of attempting to lead a chiefly intellectual life that little has been reported of such cases.* Apart from the accidents of war dysphasia is a condition encountered chiefly among those of established occupation, or those whose days of active occupation are over. The significant problems of prognosis and rehabilitation scarcely go beyond the question of whether or not the patient can maintain and exercise skills long since acquired—skills whose progressive aspects may for some time have fallen into abeyance. And the analysis of intellectual deterioration and its relationship to linguistic breakdown is much complicated by the existence of ingrown habitual practices, whose disentanglement from constructive adaptations is not easy to effect. The case of a healthy and highly intelligent young man, destined for one of the learned professions and educated accordingly, who becomes the victim of dysphasia between school and university, is, however, a very different one. He presents, for instance, prognostic and rehabilitation problems of great delicacy: if encouraged and enabled to pursue his earlier plans of becoming a university student, he will be engaged for at least two years in work that is continually novel and constructive, and almost exclusively intellectual. Moreover it is work which demands the written expression of thought upon a succession of occasions. The study of this written material, in conjunction with a clinical assessment of his condition throughout the period, can scarcely fail to be of interest. Not the least interesting is the relation of thought to language, especially the question of how far there is interaction, and how far mere parallelism, or independence, in their breakdown and recovery.

*In Head's (1926) series, for example, one patient is reported to have had a university education, and one to have been a medical student before injury. In neither of these is there any suggestion of their return to intellectual occupations. In one other case (No. 2) it is reported that the patient re-learnt Hindustani, and in general showed a remarkable power of re-acquiring knowledge. Head remarks that he might superficially have passed for a normal man. Alajouanine (1948) gives an interesting account of three cases of dysphasia in elderly people who had followed intellectual or artistic vocations. Only one of these (an artist) was able effectively to continue his previous activities.

Case History

Lieut. K (Case No. 16134), who came of a professional family, was educated at a public school and won an open scholarship to the university before joining the Army in 1942. His chief interest at school had been in classics, and he had intended continuing their study at the university, though he had actually won his scholarship in history. After sustaining a head injury he found difficulty in recalling Latin and Greek, especially the latter, and this fact made him decide to read history.

On September 7, 1944, at the age of 23, the patient sustained a deep penetrating injury from a shell fragment in the left temporal region. The wound was excised and sutured on September 8, 1944, when 2–3 oz. of pulp and blood clot were removed. The wound healed by first intention. The *x*-ray tracing in Fig. 1 shows the extent of the resulting bone-defect which measured 10×4 cm. approximately. Retrograde amnesia was momentary. Post-traumatic amnesia lasted for about four weeks. On becoming aware of his surroundings he thought that he must be in a foreign country as speech had no meaning. This only lasted for a few days. He also failed to recognize his mother at first, and thought she must be a social worker.

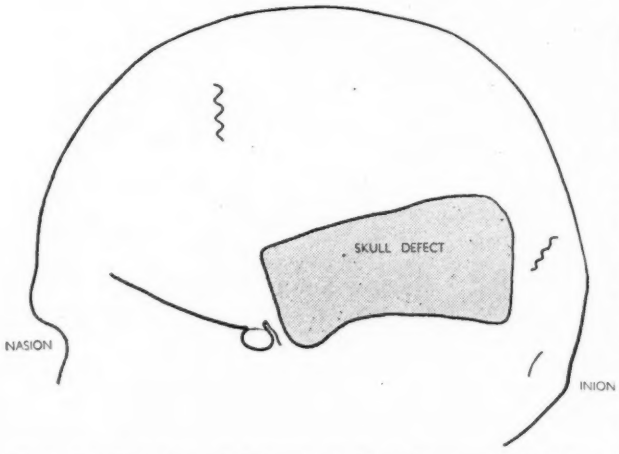

FIG. 1.—Tracing of lateral skull radiograph showing site of post-operative skull defect.

He sustained a complete and permanent homonymous hemianopia to the right. He had two fits (in December, 1945, and July, 1946) beginning in the right hand and progressing to a generalized convulsion. He is still (1950) taking phenobarbitone. For a brief period after the injury he suffered from complete right hemiplegia, but this had cleared up by December, 1944. The available evidence suggests that he was predominantly right-handed, though he had played tennis with the left hand, and was in the habit of using it for a few other activities.

By the time he entered the university in the autumn of 1945, the paralysis and the speech were much improved. He was able to row in his college boat and to take a fairly normal part in university life. In December, 1946, however, he still used a stick in walking, partly because he was not fully adjusted to his hemianopia (and complained of a wandering right eye), and partly because his right foot was still troublesome. Speech in December, 1946, was rapid (as it had always been, he said), and very irregular in tempo. He felt difficulty in framing what he wanted to say, and this was increased by any delay or any attempt to think over the expression of his ideas before utterance. The urgency of his speech decreased during the two and a half years that followed, but was still noticeable in June, 1946. The hemianopia remained essentially unchanged. He appeared eventually to make a good adaptation to the difficulty. By the time he left the university, the complaint of a wandering eye had ceased, and he was able to move about normally.

He remained at the university for seven terms, and was placed in the second class in the final honours examination for the shortened war course. For about six months afterwards he worked in a museum as a student, with the idea of looking for a job in a local history museum later. Difficulty in being accepted for insurance cut short his efforts to obtain such work under a local authority, but in the autumn of 1948 he was awarded a research studentship in London seventeenth century history. The award was for one year and has been renewed once.

In December, 1946, he was given a number of psychometric tests. On the Wechsler-Bellevue scale his vocabulary was at a very superior level, and there was no impairment in arithmetical computation and reasoning, in immediate retention for digits, or for visual-constructive tasks. His weighted scores were : vocabulary, 18 ; arithmetic, 17 ; block-designs, 16. On the digit-symbol sub-test his performance was relatively poor, his weighted score being 8. Immediate retention for verbal material was above average, though, presumably, relatively constricted for his general intellectual level, and he found considerable difficulty in learning digits or verbal material beyond his immediate retention span. Immediately after reading a passage through he could recall a number of items nearly as great as the norm, but he felt the task to be difficult, and his performance was poor in relation to his general ability. He could reproduce argument more correctly than narrative. For both these types of material reproduction was more coherent after five minutes delay than immediately after presentation, although some points might be forgotten in the interval. On neither the sorting (Vigotsky) nor Rorschach tests were there any marked peculiarities, though on the former there was some tendency to abandon one principle for another before completing the sorting, and on the latter his drive to organize his ideas tended to be poorly maintained. In verbal reasoning (Burt-problems) he was generally quick and correct, but would sometimes overlook a detail in the longer problems and then find it difficult or impossible to spot his omission on re-reading. He was also inclined to become too involved in his own view of the problem, either as regards form or matter, to be able to return to the facts as stated, despite a real effort and intention to do so.

At this time comprehension of speech in ordinary conversation seemed normal. When required to sort objects according to a verbally formulated dichotomy he made no errors that he did not himself correct in 70 choices, but obviously found the task exhausting. His spontaneous speech was rapid, though punctuated with many hesitations, some a—a—a-ing, and some repetition of initial s's. In answer to specific questions speech became more hesitant and awkward. Pronunciation was correct, and there was no actual misuse of words in conversation. He showed some hesitation in naming objects. Finding the word he wanted when trying to express an idea of any complexity, as in giving a definition, was a task of some difficulty. Reading aloud was accurate except for a slight tendency to drop or alter the endings of longer words, and to confuse short words such as " to ", " the ", " for ", errors which he generally corrected. Hesitations were conspicuous and were associated with an inability to see what lay ahead, the consequence of his hemianopia. Difficulty in comprehension only appeared in dealing with long and involved statements where visual and retentive disabilities seemed to be of considerable consequence. His speed of comprehending visual symbols briefly presented seemed to be normal, although the right half of the field was frequently missed. Given the time to think of each word, spelling was good, though he was apt to be doubtful of double letters. Writing was rapid, legible, and grammatical. When tired, however, he was still apt to misuse words, and commit grammatical errors.

Such disabilities became evident in writing long essays, though not in the test interview. He described his memory for events in the recent past as vague, and found it difficult to recall much of what had happened during the previous summer holiday which had been spent abroad. He complained of a liability to make conflicting appointments, and then forget both.

In the past, his interest had quite largely centred around verbal activity. Words amused him, and he was given to playing with them in epigram and rhyme. He met his linguistic difficulties in good spirit, created social capital out of jokes about his speech errors, and made considerable efforts to adapt his ambitions to his now restricted capacities. (He had originally intended to read for the Bar.) He entered into all the social, intellectual and athletic activities of which he was still capable. In December, 1946, however, he was very conscious of the difficulty he was finding in learning and remembering, and in writing satisfactory essays. He became somewhat distressed by his inability to use notes made on his holiday reading on account of their incomprehensibility. And in general he was wondering in an anxious way about his prospects. After a careful clinical and psychological assessment, however, he was encouraged to continue reading for his degree. At this time he very kindly agreed to submit for study some of his written work.

The Written Material Submitted for Analysis

The written material selected for analysis was the following: (1) an essay written in his last term at school before joining the army; (2) two letters written in November, 1944, three months after injury; (3) eight essays chosen from those written each week between October, 1945, and June, 1947; (4) two trial examination papers; (5) an essay written voluntarily at our request in January, 1948, six months after taking his degree.

Analysis of the Material

General.—The following quotation from his school essay is given as an example of his written work before his injury. It was written at the age of 17 on " The Conquest of Egypt ".

> Now the Cabinet was faced with the decision of leaving Gordon to his fate, or sending a large army to save him. They had not the courage to do either. At last public opinion forced them to send Wolseley to get him back. Wolseley reached Egypt, battled his way up the Nile, sent forward advance guards and pushed on for all he was worth. A minor reverse held them up for three days. They reached Khartoum two days after Gordon was killed.

No spelling or grammatical errors occur in this essay which is easy to read, intelligent and coherent, though not brilliant. Language is used with facility and some dramatic effect. At the same time it ought perhaps to be noted that a few minor defects of expression are shown, and these are of a kind which occurs in a much more severe form in the later material. It would be more correct in the last sentence to say " . . . after Gordon *had been* killed." And, in the two preceding sentences, there is a certain confusion of number which leaves the meaning rather imprecise.

Extracts from two letters indicate the degree of difficulty he experienced in written expression three months after the injury.

> I hope this will come to you for the right address I am attempting. I do want to hear fo you and how you are making as it is ages since I heard of you since the last I spoke to you.
>
> As you bullied me to promise a letter, I will do so and do youself as good as mine will be. A Very cryptic remark? I'll have to get on to you. How are you? Do you. answer? No? Well the answer doesn't matter.

There are examples here of the use of omnibus words (e.g., " do " and " make ") to cover limitations of vocabulary, of the misuse of prepositions (e.g., "*for* the right address "), of repetitions and omissions, and of a change of grammatical structure in the middle of a sentence.

The first essay was nearly incomprehensible without much re-reading, interpolation, and interpretation on the part of the reader. For the following six months essays continued to be very difficult to follow. Nevertheless, from the beginning they were shapely. A basic pattern of introduction, argument, and conclusion could, with sufficient effort, be seen to emerge from the matter, although the proper connexions between paragraphs, and often between phrases and sentences, were not expressed or were expressed incorrectly. Some measure of real comprehension and planning must have been applied in writing the essays from October, 1945, onwards, even though the patient felt that he had not " really understood the subject ", and that his own essays were of little use to him in refreshing his memory. The difficulty he found in using his essays and the notes he took on reading during the summer of 1946, was, however, only in part due to their " incomprehensibility ". By June, 1946, the essays were, in fact, moderately clear and coherent despite errors. But in re-reading such essays, though he found the opinions expressed clear enough, he was disturbed by the apparent vagueness of the facts, and by the failure of what he had written to bring them to mind again. Consequently he had to re-study each subject for examination purposes. By contrast, he found himself able to recall opinion, but in December, 1946, he could never be sure whether it was his own opinion or somebody else's. By 1950 he was sure that it was in fact always his own opinion that was so recalled.

Essays written up to the end of 1946, and indeed into 1947, were written quickly in order to put his

ideas down before he lost the gist of what he wanted to say. On the whole he felt that they were the more coherent the quicker he wrote, and the less he really had to say. On the other hand spelling mistakes and minor omissions were more likely to occur with speed. When reading the essays aloud to his tutor he could, and would, make alterations and corrections. Nevertheless, it was not until the late spring of 1946 that his tutor felt that he began to see " what the essays were driving at ". During the autumn of 1945 he was writing two essays a week on different periods of history, one on the Restoration in which he was interested, the other on the Anglo-Saxon period in which he was not. The periods were about equally new to him. The first group of essays are the harder to follow, but have more substance and show more evidence of thought. The latter are simpler, shorter, more factual, and are expressed in a rather juvenile way.

Length of Essays and Errors.—Table I shows the length of the representative essays, together with the types of error. Though there is no steady increase, and it would be unreasonable to consider such an increase to be in itself a sign of improvement, the last essay of the university group is in fact nearly twice the length of the first. The last, also, has fewer errors than the first, and the majority of the minor errors occur towards the end, possibly indicating fatigue.

In order to allow comparison throughout the series, the original numbers have all been converted into the number of errors per 10,000 words (to the nearest whole number). An interesting point which emerges from Table I is that the trend of improvement is marked most clearly in the fewer wrong prepositions, and in the decreasing number of awkward, indeterminate expressions, and spelling errors. In other cases, those for instance of the use of the wrong verb, and of a shift of grammatical form, no clear trend is present at all, unless it consists in a tendency for performance to be at its worst in the *middle* of the series of essays. Total errors are shown graphed against time in Fig. 2, and prepositional errors in Fig. 3.

Spelling errors decreased, on the whole, during the year and a half covered by the essays for tutorials, but there was a sudden increase when limited time conditions were imposed as in the trial paper (No. 9). This seemed to indicate lack of time for correction, rather than renewed breakdown due

TABLE I

PROPORTIONAL ERRORS IN A SERIES OF ESSAYS

Essay Number	Date of Essay	Number of Words	Wrong Preposition	Ambiguous Relation of Preposition	Number of Verb or Pronoun Wrong	Wrong Tense of Verb	Wrong Form of Verb	Wrong Verb	Neologism	Omission of Verb Group	Minor Omissions	Repetitions	Shift of Grammatical Form or Idiom	Awkward Expression Making Meaning Indeterminate	Spelling Errors	Totals
1	October, 1945	1380	72	7	22	7	29	7	0	7	22	7	—	72	80	332
2	January, 1946	1495	34	7	7	7	7	7	13	0	0	7	13	67	60	229
3	May, 1946	2100	10	0	0	0	10	10	0	10	5	5	0	19	38	107
4	June, 1946	2200	23	0	18	0	0	0	0	5	14	0	5	9	32	106
5	October, 1946	2114	10	0	24	0	5	14	0	0	18	5	5	10	10	101
6	December, 1946	1605	13	0	6	6	6	6	0	6	6	6	6	6	0	67
7	January, 1947	1605	0	0	13	6	6	25	0	6	0	0	13	0	25	94
8	February, 1947	2537	20	4	20	0	12	8	0	4	20	0	8	4	20	120
9	January, 1948	1500	7	0	14	0	0	7	0	0	0	0	0	14	7	49
	Total		189	18	124	26	75	84	13	38	85	30	50	201	272	1205

to fatigue or strain. The errors appear scattered throughout the paper, as they do in the essays written

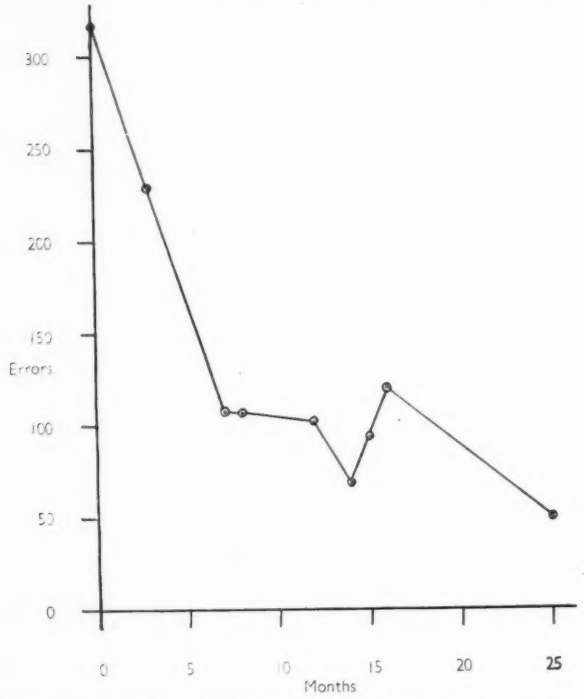

FIG. 2.—Graph of total errors in the series of essays.

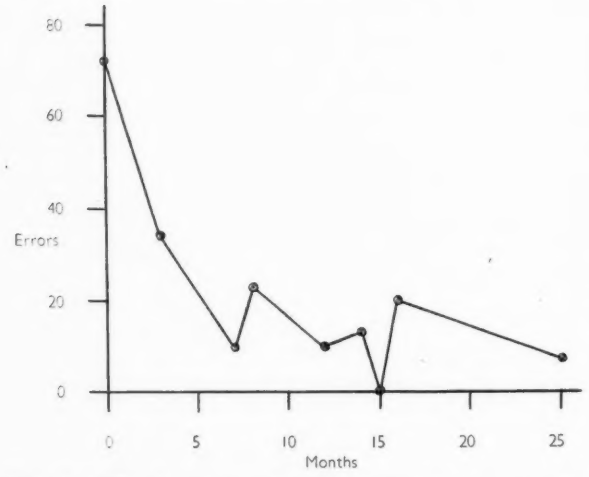

FIG. 3.—Graph of prepositional errors in the series of essays.

at leisure, but in the latter they would generally be corrected on re-reading. The only uncorrected error in the voluntary essay of January, 1948, is " dependant " for " dependent ", one so common as to be of little significance. In any case, the patient provided written evidence that his spelling before injury had not been flawless.

Vocabulary.—Table II shows the number of different words used in the first 994 words of essays 1 and 8, analysed according to parts of speech. These figures show a 67% increase of vocabulary over this period, and this is in keeping with the great decrease in verbal repetition noticeable in the first essay.

" . . . changes were *made* to *make* the Castles under Royal *Control* . . . soon to *make* Pitt in *control* ".

" . . . *consummation* was *consummated* ".

" . . . parties were *continually pressed* by the *continual pressure* of the Crown ".

Secondly it appears from this table that nouns and adjectives show the greatest absolute, as also the highest percentage, increase. The relative numbers of parts of speech, however, remain remarkably constant. The more precise denotation possible with the greater range of nouns and adjectives brought into play is reflected in the abatement of confusion caused by the use of over-general words. Conjunctions also show a high percentage increase, doubling in number during the year and a half, and this allows a much more explicit relation of ideas. A considerable increase in adverbs, many of them temporal, had the same beneficial effect.

The actual misuse of conjunctions was comparatively rare : the relations between sentences and clauses were more commonly left unexpressed. In this respect conjunctions differed considerably from prepositions. The latter increased only slightly in variety (they were rarely omitted even in the earliest essays) but their misuse was constant at first, tended easily to recur with fatigue later, and was not entirely eliminated even by 1948 in the voluntary essay written at leisure. The reason for this difference is not clear, though it might perhaps be suggested that omission of conjunctions is not so destructive of the formal structure of the sentence as is that of prepositions.

It must not be supposed, in analysing the patient's vocabulary at a given stage of recovery, that his restricted use of words was wholly the product of their loss or unavailability. Perseverative tendencies, both in respect of words and of phrases, may prevent the employment of words which would otherwise play a part in his expression.

Major Factors Causing Incomprehensibility.—The chief factors which make the early essays difficult to understand are the following.

The Misuse of Single Words.—The construction following such a word is often not anticipated by the reader.

" The State church *became* not under State control."

TABLE II

VARIETY OF WORDS USED IN ESSAYS 1 (OCTOBER, 1945) AND 8 (FEBRUARY, 1947)

Part of Speech	Essay 1		Essay 8		Absolute Increase	Percentage Increase
	No. of Different Words	Percentage	No. of Different Words	Percentage		
Articles..	3	—	3	—	0	0
Prepositions	19	5	22	4	3	16
Pronouns	11	3	15	3	4	36
Nouns (Proper) ..	25	7	43	7	18	72
Nouns (Common) ..	115	31	197	32	82	71
Verbs	70	19	95	16	25	36
Adjectives	77	21	160	25	83	108
Adverbs	33	9	52	9	19	58
Conjunctions	12	3	24	4	12	100
Total	365		611		246	67

" . . . *of* its negative attitude, the most important problem arose . . . "

" The Commons had long been at issue *over* the Crown on matters of finance."

Failure to State the Main Point of a Paragraph.—Comment and criticism are given without adequate indication of the subject.

Lack of Verbal Precision.—Too often " general " words are used, when a wider vocabulary would have provided the right word in the right place.

" The *negative aspect* of Parliament . . . "

" He was in all *things* supreme."

" . . . failure of negociations encouraged Cromwell to *let the matter turn* into war."

" Yet he *brought about* an even more powerful *disrupting factor* to the Whigs."

A similar fault is the failure to qualify a reference sufficiently :—

" Whig theory " (referring to the Whig theory of an aristocratic Junta).

" They fell back on the 1640 attitude."

Inappropriate Use of Words.—This seems in part to be simple perseveration, affording a solution to the difficulties of a restricted vocabulary, but the patient's delight in epigram perhaps also encourages the tendency.

" . . . parties *reversed* in their attitude to external affairs . . . systems of electoral representation was not *reversed.*"

" . . . not examine *details* [i.e. to judge the value of Wolseley's later work] but the results. Then later . . . the *details* of his work had more effect."

In the second example the logical failure is only apparent. In fact the second " detail " is short for " the effect on detail ".

Telescoping Ideas.—There was a tendency to telescope ideas, and their logical connexion either of content or grammar was omitted.

" . . . final outbreak of disturbance that caused Henry to submit was his own contact with foreign affairs."

Such telescoping may apply to an alteration in the writer's point of view, and will then often involve a change of grammatical structure.

" The long eclipse of the Whigs only emerged when a Whig Party under Grey was built up."

In many cases, especially in the first term's essays, the awkwardness was composite in origin, and could be subsumed under more than one of the above headings.

" The existence of James as a Roman Catholic intensified by his marriage . . . "
(Shift, telescoping, ? omission.)

" It made pressure of the Crown brought to a head but it did not clear the issue."
(Omission, misuse of word, ? shift of approach.)

" The final failure of North made the King *to* surrender at last " followed by " . . . by refusing to allow a Parliament to be held in his absence he at once *made* any such Parliament to *be* obviously rebellious."
(Over-general words, ? shift in construction.)

Minor Errors.—In addition to these major sources of confusion, there are other types of error. These, though less confusing to the reader, demand alertness if they are not to be allowed to disrupt the meaning. Among these minor errors are the omission of minor words, the ambiguous relation of pronouns, word repetition, the use of an incorrect grammatical form or of a wrong tense, failure to make verb or pronoun agree in number, and minor shifts of grammatical construction not in themselves very confusing.

Condition at the End of the Essay Series

In March, 1948, the patient was given the digit symbol test again. He made six more substitutions, and the same two half errors as he had in December, 1946. Though there had been a great change in his general adjustment to the field defect during this time, it probably still handicapped him on a test of this type. By this date, his immediate retention span for verbal material had increased so that he could repeat the appropriate Babcock sentence with ease. Verbal learning beyond this span, however, still presented difficulty. He no longer had the trouble in reproducing a moderately complicated grammatical structure that he experienced in December, 1946. At that time he was apt to introduce alterations of a mildly confabulatory nature which were based, apparently, upon the use of visualization to surmount verbal difficulty. In March, 1948, these were no longer evident. But omissions of structurally important words occurred, as did the introduction of synonyms. These errors tended to recur in a perseverative fashion. He was, however, able to reproduce the content of verbal passages more coherently and fully. An increased capacity for rote retention assisted him in this, but he was still liable to rely upon a word sequence rather than upon retention of the trains of ideas expressed. When this tendency led him into absurdity he would correct himself. He showed an improved capacity to carry out verbal reasoning tests of the type devised by Burt. He clung less tenaciously to his first incorrect conclusion, and on re-reading the problem more quickly grasped relevant data previously overlooked and so was able to consider its implications without getting confused with his previous line of reasoning.

In February, 1950, he reported some difficulty in learning new technical terms. He complained that he constantly forgot the sources of his information, and had in consequence to make frequent fresh starts. Dates, even when he was constantly using them, slipped easily from his mind. As regards day-to-day memory, he found that he was still inclined to forget appointments, though less frequently than three years before. He had a " permanent uncertainty about the date and the day of the week ". His memory of the past was, he said, more complete and accurate than it had been, though recall did not produce much " emotional excitement ", perhaps because the work he had been doing was unexciting compared with his activity during the war years. The contrast between war and peace made comparison difficult, but he thought that he lived " very much from day to day . . . with little sense of anticipation in that I do not make any advance plans, and the fact that I am going to do or see anything new does not produce any excitement ". Events during the war " have a far sharper photographic impression on my mind ".

He was seen again in November, 1950, and there appeared to have been little change in his condition, in so far as it could be elicited by interview and a few psychometric tests. His speech was still subject to blockages demanding the introduction of circumlocutory and redundant material if the flow of expression was to be preserved. Object-naming was not free from error and circumlocution. The written expression of material just studied by reading was very adequate, but was carried out at a furious speed. He made a few spelling errors, mostly corrected, chiefly of substitution of phonetically similar consonants. Grammar, syntax, and logical form might be regarded as normal (if sometimes slipshod), considering the haste with which the tasks were carried out, and the written versions showed evidence of intelligent compression of the originals. He again noted greater ease in reproducing argument than narrative, and this was borne out by his performance. On the digit-symbol test there was evidence of a further slight improvement, his weighted score having risen to 11.

On questioning him regarding his present life and work, much the same points were elicited as on the previous occasion, and indeed it seemed that he had reached a stable attitude towards himself and his affairs, so that he confines his activities to those in which he can reach an adequate level of adjustment or achievement without drawing upon the finer points of skill which are now impaired. How successful he is in carrying out his historical work it is impossible to say, but it is certainly of a character which intellectually would have made but slight demands upon a person of his intelligence if unimpaired. He himself feels that his present capacities are adequate to his work, but acknowledges that his overall rate of working is probably no more than a third of what it was previous to injury. He is frequently constrained to break off

work and turn for a time to a distraction such as *The Times* crossword puzzle (which he finds himself quite competent to tackle). In short, he appears to have reached, at least temporarily, an adequate, if constricted, adaptation. Whether this phase will be succeeded by one of fresh expansion remains to be seen.

Discussion

We have already remarked upon the meagre fruits of theory about the relations of thought and language. John Dewey (1933) has said: "The conviction that language is necessary to thinking (is even identical with it) is met by the contention that language perverts and conceals thought", and, he continues, broadly three different views have found their supporters. The first is that the two are identical. The second that words are necessary only for the communication of thought, not for thought itself: the third that language, though not identical with thought, is yet necessary to it. This last, commonly upheld, must at once raise the question of the precise manner in which language plays its role in the processes of thinking. In the special field of linguistic breakdown, this question becomes, "In what way does a disturbance of the language mechanisms impede thinking?" and, "Is the disturbance of thought capacity in dysphasics thus *only* secondary to the language breakdown?"

To these questions, Henry Head offered one possible answer. For him, whatever is worthy of the name of thought is not an act of "simple matching", but demands the intervention of symbolic processes between stimulus and response. Aphasia is basically a disorder of these symbolic mechanisms. That it manifests itself chiefly in the linguistic field is but a reflection of the predominance of language among the other symbolic systems used by man. The patient is "lame in thinking" because the mechanisms by which he thinks are out of order. In somewhat similar fashion, the economic life of a country would be very gravely disturbed if its monetary and banking system were largely destroyed overnight. The movements of currency and credit do not *constitute* trade. Barter operations, though clumsy and limited in scope, are possible without them. But in practice a monetary and banking system is necessary to modern commerce as we know it. Without it, too, payments in actual coin become meaningless. So, for Head, both disturbance of thought and breakdown of overt language alike arise from the destruction of the more basic symbolic mechanisms. His conclusion is, perhaps, chiefly of value in its emphasis upon the immense complexity of the processes which underlie both thought and language, by contrast with the relative simplicity of the verbal transactions we observe. Sentences, like payments in actual coin, are limited in variety by the available material. Neither reveals the richness of the organization behind them.*

Other writers, of whom the outstanding example is Arnold Pick, have approached the problem of the relation of language to thought in somewhat different terms. They have asked by what sequence of processes the thought is formulated into a sentence suitable for overt expression. As expounded in his earlier work (1913) these comprise four stages: (1) the mental attitude, diffuse if intellectually informed; (2) the thought-*schema*, in which the material is psychologically differentiated; (3) the *schema* of the phrase, in which the syntactical and grammatical form of what is to be uttered is present; and (4) the choice of words to fill in the phrase-*schema* and complete the sentence. Pick's justification for the adoption of this kind of framework† lies in his conviction that clinically the varieties of aphasia are in accordance with it. Certainly it emphasizes the difference between those disorders which manifest themselves chiefly in a disturbance of content, and those, such as agrammatism, where the disruption is one of form.

Useful as conceptions such as these may be in the analysis of language disorders, they are clearly incomplete inasmuch as they offer little in the way of hypotheses regarding the manner in which thought itself takes place. The views of Selz (1922, 1924), who obtained from experiments on the thought-processes themselves independent evidence of the part played by schematic frameworks, go some way towards extending Pick's findings in the required direction. Bartlett's (1932) extension of Head's theory of *schemata* is perhaps equally relevant.

But, apart from the shortcomings already noted, current theories in this field suffer from another grave defect, and it is this which observations on our patient throw into relief. "As soon as we attempt to express our thoughts even to ourselves," writes Head (1926), "we re-arrange them and drastically prune away redundant and incoherent features. For the purpose of articulated speech or writing this process is carried out still more ruthlessly . . . the results of unrestricted thinking are refined and ordered in accordance with logical canons." Certainly this is one essential aspect of the formulatory

*It should, perhaps, be made clear that Head did not employ this economic analogy, but it seems not inappropriately to express the essence of his view.

†Pick is at some pains, especially in his later writings (1931), to make it clear that this sequence of stages is flexible, and by no means always fully followed. There may, for instance, be condensation, and thought may proceed at levels other than the first. Van Woerkom (1921) has proposed a similar set of stages, which places greater emphasis on the active—synthetic and analytic—nature of the second stage.

process. But there are others, less comforting in their implications, which have not received the attention of which they are worthy. At these Head hints when he remarks: "The superb logician may have difficulty in expounding his ideas and we are familiar with the practised speaker whose words are jejune of thought". The introduction of coherence and the pruning of redundancies are too often not the sole outcome of formulation. Something may be lost from the thought itself. Habitual verbal forms, and conventional syntactical schemes, eagerly offer themselves, as Delacroix (1924) and others have pointed out, to spare the pains of thought. The element of originality or profundity the original shadowy thought perhaps possessed may be beyond the skill or patience of the speaker to formulate. Instead a compromise completion of the task is reached, in terms of empty and conventional, if sometimes elegant, expression. This tendency will be reinforced where, as is frequently the case with expressive dysphasics, continuity of utterance is imperative if breakdown and blockage are to be avoided. Alternatively, something of the essence of the thought may be preserved only at the expense of obscure and complex verbal guise which, even in the normal individual, may amount to syntactical error. There is a basic antagonism between thought and expression which always demands some compromise. There may be conflict to the extent that the individual's aspirations become involved on one side or the other.

When we consider the series of essays written by our patient, we may ask how far defects of expression can be distinguished from those of thought, and to what extent both can be seen to be the outcome of some common failure of intellectual organization. As improvement takes place, do the two types of difficulty clear up in parallel fashion? It may be remarked at once that, while the evidence points to a general parallelism of progress, there are occasions when his thought appears to be clearer and more adequately structured than his faulty language allows him to express. On others a deceptive clarity of expression may conceal an underlying woolliness of thought. That thinking was often clearer than expression was demonstrably true when prepositions were misused and conjunctions omitted. He was frequently prepared during 1947 to defend his misuse of prepositions, at the same time indicating in other ways that the idea was perfectly clear. He could explain the relationship of phrases and sentences which he failed, by omitting a conjunction, sufficiently to relate. Similarly the denotation of many over-general nouns and expressions was in fact more precise to him than might appear to the reader, as would become clear from his amplifications in conversation. The same could be said of some telescoping and shifts of grammatical structure. Confused expression at any particular point, in fact, did not necessarily indicate a corresponding confusion of thought. It was often simply the outcome of the inadequate linguistic resources available to him at that moment. The actual expression achieved would then be a compromise reached by lowering his standards of correctness, and even by the acceptance of pathological tendencies such as perseveration. On the other hand, expression could superficially be clearer than thought. The clearest of his early essays were those about subjects in which he was not strongly interested. According to his own account he would, in such cases, take the leading ideas from his reading and reproduce them glibly without much comprehension of their implications and relations. Something which did not engage his personal intellectual interest equally did not evoke the repressive criticisms and linguistic inhibitions which few normal writers escape. In his own words:

> "I could see that there were ideas A, B, and C. I could use A, B, and C in an Euclidean way, finishing up with a Q.E.D., without really knowing what A, B, and C implied. For instance, I might have known that growth of the powers of the *thegns* was an important fact, and that this led to the success of William the Conqueror. But I would not have seen why it was important, nor would I have any idea how, when and why the *thegns* had become important, nor even what I meant by *thegn*. I don't now. But I could put down correctly A+B+C=D. It certainly meant that even at the time of reading my sources I didn't really understand the point, though I could see that it was one."

Clearly some comprehension is needed to make a sensible selection of points, and to follow a plan A+B+C=D. But his understanding of the situation was superficial, hardly going deeper than a commonplace acceptance of the verbal terms of the argument and of their logical outcome. Expression was coherent but simple.

It is not without interest to compare the peculiarities of the patient's verbal expression with the difficulties of thought which he experienced, as judged by the quotation. A number of parallels suggest themselves.

There is a correspondence between the tendency to use words of over-general meaning in expression, such as "matter" and "thing" (associated with a small number of substantives and adjectives in the earlier essays), and the lack of specificity and structure in an idea; for example, the lack of explicit understanding of what thegns were and did, notwithstanding the appropriate use of the word thegn in argument.

The inadequate articulation of sentences, clauses, and paragraphs which results from a paucity of conjunctions, the wrong use of prepositions, and the omission of connecting statements, may perhaps find a parallel in the incomplete connexion of ideas which he describes when, for instance, he remarks that the importance of the growth of the power of the thegns was not evident to him. His thinking lacks the formal precision which in expression is afforded by the words " therefore ", " now ", " because of ", and " on the other hand ".

The changes in grammatical structure which are apt to occur part of the way through a sentence (" forgetting how a sentence started ") might be held to correspond with the difficulty experienced in keeping a total problem in mind while still considering the implications of part of the data. This difficulty was shown in his performance on the verbal reasoning tests. It is also indicated in his feeling that much reading was a bad preparation for writing the essay (" The less preparation and reading I do, the better the essay ", 1946).

Speed, both in achieving expression and in understanding a situation, were of great importance to him. Fear of forgetting the beginning, whether of a sentence or of a train of thought, was one element in his desire for speed. Another was the avoidance of interference by the search for appropriate words on the one hand, and by the seduction of intellectual red-herrings on the other. The structure of both speech and thought was to some degree evanescent. In thinking he sought for structures ; for instance he complained of the lack of a clear chronological framework in Anglo-Saxon history on which to hang events. In the effort to replace the insight which he lacked, he would adopt an artificial structure not really grounded in his thought, and this would often prove inadequate to the solution of the particular problem he was engaged on. In the same way, the grammatical structure of the beginning of a sentence was apt not to anticipate its end appropriately.

Coherence in thought and speech had their best opportunity if deliberation were avoided. Deliberation might involve, for instance, search for an appropriate word, or the consideration in greater detail of evidence hitherto partially neglected. In these cases confusion was likely to arise. But, characteristically, this inadequacy of structure resulted in rigidity rather than in weakness of thought and expression. If, in reasoning, a form grew out of the data, it was difficult for the patient to treat it as tentative. Either it broke down when further evidence was noted, or it persisted rigidly and contra-indications were ignored. In verbal expression, the tendency to rigidity appeared in the form of stock phrases, of phrases personally favoured by the patient, or of phrases recently used. These were the alternative to breakdown of expressive activity. Both in thought and expression, the patient seemed to lack normal freedom to manipulate his own mental processes. The healthy individual can and does treat each production of his mental activity as the object of criticism and refinement, so arriving at an apt response. The patient cannot achieve such smooth convergence upon the appropriate act. If he is to decide, or to express, at all, it can often only be done by accepting incompletely evident concepts, or inaccurate grammatical forms.

Certainly in general the patient gave evidence of corresponding difficulties in the field of thought and expression, but it is at the same time clear that these two skills are to some extent independent of one another, inasmuch as the compromise in his performance might be reached at the expense of one or other of them. The freer he was from the intellectual difficulties aroused by his own interests, the greater was his capacity to express himself correctly. Where, on the other hand, his more personal intellectual powers were challenged, all his expressive disabilities were aroused in the effort to do justice to his thought.

These considerations suggest, perhaps, that where the attempt is made to re-educate the dysphasic by exercise in expression, the subject matter should be chosen so as to evoke interest, but not touch too closely the more basic of the patient's preoccupations. Where, on the other hand, it is desired to rehabilitate the capacity for thought, too close an insistence on its formal expression may defeat the main object.

Our main conclusions which emerge from the study of this patient's behaviour are.

(1) The common basis, which Head attributes to the intellectual and linguistic functions is borne out in so far as both in their breakdown and their recovery they exhibit phases of a broadly similar character. It must be remembered in this connexion, however, that the dysphasia exhibited by our patient was of a predominantly expressive character, and any assessment of his thinking is therefore to some extent conjectural. Nevertheless it has seemed to us possible to distinguish to some extent the respects in which his difficulties were to be attributed to breakdown of the symbolic mechanisms utilized in thinking from those more especially connected with linguistic expression. But it is clear that, according to Head's view, no *absolute* distinction of this kind can be made.

(2) The implicit, unavoidable, conflict involved in the attempt to formulate and express the products of thought is more clearly shown in a patient of this

kind than in the normal individual. The resulting compromise is less apt, sometimes doing justice to the thought at the expense of clarity in expression, at others accepting conventional forms of expression which replace the thinker's individual contribution by socially contrived clichés. In the latter case it is later difficult, as he reported, for the patient to decide whether the views so expressed are his own or those of others.

(3) Progress in the restitution of expressive function, as shown in the essay series, is clearly marked by a decrease in prepositional errors, and it is suggested that this is paralleled by increasing capacity to use valid structures in the manipulation of ideas.

Summary

The case is described of a young, healthy, and highly intelligent man who sustained a penetrating head injury producing an initially severe dysphasia, and subsequently took up the open scholarship he had previously won at the university and obtained second class honours.

A number of the essays which the patient wrote as a student are analysed and his progress traced in respect both of linguistic and intellectual skills. His condition was also assessed at intervals clinically and by psychometric methods.

Linguistic and intellectual improvement showed a parallel course, but the effects of the antagonistic demands of thought and expression were also noted.

Some consideration is given to the bearing of the findings on current views regarding the relations of language and thought.

We should like to express our gratitude to the patient for his generosity in making his written work available for analysis, and for his ready response to all our enquiries. We have also to thank Sir Hugh Cairns and Dr. W. Ritchie Russell for permission to make use of the clinical material, and to publish this case.

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A CASE OF GUSTATORY SWEATING

BY

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Profuse facial sweating on eating is a rare phenomenon of interest not only as a clinical problem but also as a means of elucidating the complex mechanism of the nervous and hormonal control of perspiration. Of the cases described hitherto all except one have occurred as a result of sympathetic paralysis particularly in the distribution of the auriculo-temporal nerve. The present case is unusual in having no such predisposing cause and in presenting some unusual features on investigation.

The usual story is that an injury to the sympathetic supply to a part of the face is followed after an interval of anything from a few days to several months by sweating, of varying degree, on eating. Investigation confirms the deficient sympathetic supply and shows that certain drugs like acetylcholine and pilocarpine which normally cause sweating on injection produce an excessive response. The one case in which no sympathetic paralysis occurred was a patient with syringomyelia (Wilson, 1936).

A variety of explanations has been offered for the phenomenon of gustatory sweating. The sensitivity of the sweat glands to acetylcholine suggested that sweating might be due to a diffusion of this substance from the cholinergic nerve endings during reflex salivation (List and Peet, 1938). On the other hand it was suggested that since section of the sympathetic nerves had taken place there might have been abberrant regeneration in which other cholinergic fibres, say salivary fibres, came to supply sweat glands so that there would be a sweating response to any stimulus to salivation (Ford, 1933). Yet another suggestion was that there might be a double innervation to the sweat glands of the face, since sweating, which could be inhibited by peripheral nerve block, was seen to occur in an area where the sympathetic nerves were known to have degenerated (Wilson, 1936; Guttmann, 1931). Unfortunately none of these explanations can be applied to the present case in which, as will be shown, sweating appears to occur in response to stimulation through normal channels.

The Physiology of Sweating

The present view on the physiology of sweating (Kuno, 1934) is that generalized sweating is a response to stimulation of centres in the brain and spinal cord by emotional stimuli from the higher centres or by a rise of internal temperature due to exercise or warm surroundings. The fibres supplying the sweat glands of the face are anatomically sympathetic fibres which are nevertheless cholinergic (Dale and Feldberg, 1934). They arise in these centres, are relayed in the lateral horns of the first and second thoracic segments of the cord. and travel up the cervical sympathetic chain to be relayed again in the superior cervical ganglion. From there postganglionic fibres go to the plexus of nerves which surrounds the carotid arteries. The fibres from the internal carotid plexus join the ophthalmic division of the trigeminal nerve intracranially while those of the external carotid plexus are given off at various levels and join the second and third divisions of the trigeminal nerve extracranially. The sweat fibres are thus distributed with the terminal branches of the trigeminal nerve. No significant number, if any, is carried in the facial nerve (List and Peet. 1938) and none at all in the terminal branches of the arteries to the face (Wilson, 1936). Since the sweat glands are innervated by cholinergic fibres it is natural that acetylcholine and parasympathomimetic drugs such as mecholyl should produce sweating on subcutaneous injection. Pilocarpine also stimulates sweating by a direct action on the sweat glands themselves (Wilson, 1934). Histamine does not produce sweating unless an abnormally high dose or an intravenous injection gives rise to such severe side effects as to cause central stimulation (Weiss, Robb, and Ellis, 1932). The new and fascinating feature in the present case is that histamine produced an abnormal and localized sweating response in small

dosage and so raised some interesting points as to its mode and place of action.

Case Report

P. M., a man aged 44, was admitted to the Western Infirmary, Glasgow, in April, 1949, for gastrectomy, following a history of duodenal ulceration since 1922.

Incidental to his peptic ulcer history, he complained of sweating on the left side of the face on eating. Sweating began almost immediately and became profuse in five minutes, remained so until five or ten minutes after the conclusion of the meal and then gradually subsided in the course of the next two to four hours. The sweating was greatest over the forehead but was also present around the eye, on the side of the nose, on the cheek, upper lip and chin, and extended backwards over the parietal region. Sweating stopped sharply in the midline of the face (Fig. 1).

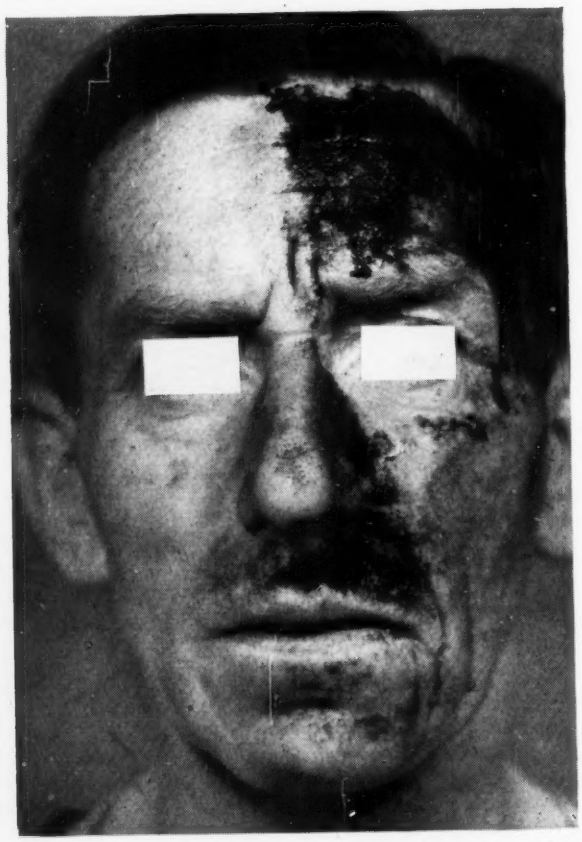

FIG. 1.—Area of gustatory sweating demonstrated by quinazerin.

The complaint was first noticed in 1946 and gradually increased in severity up to the present time when two or three handkerchiefs are required to mop the face at each meal. There was no history of injury or disease locally or referable to the central nervous system, but for the 10 or 12 years before the onset of the sweating the patient had suffered in the summer of each year from a sensitivity to sunlight which produced vesiculation on the forehead sometimes severe enough to keep him indoors. The patient is not certain whether only one side was affected, but this reaction to sunlight has not reappeared since the onset of the gustatory sweating.

On examination slight spontaneous sweating on the left side of the face was noted, especially in warm weather or following slight exertion.

There was no Horner's syndrome, the pupils were equal, and no abnormality of the central nervous system was detected. Skin temperature was taken by means of a thermocouple and was identical on both sides. The right side was used as a control in this respect throughout the observations.

A radiograph of the skull and cervical spines showed calcification of the pineal gland, choroid plexuses, and posterior clino-petrous ligaments.

The Wassermann reaction was negative.

Experiments

Investigation of the Afferent Pathway.—In the previous work on the subject there has been no important difference of opinion as to the afferent pathway of the gustatory reflex arc. In the present case it was confirmed that sweating occurred in response to stimulation of taste fibres by food and that the response was proportional to the intensity of the stimulus. The chewing of tasteless cotton wool was ineffective, showing that salivation could occur without sweating and that the exteroceptive and proprioceptive fibres of the trigeminal nerve played no part. The application of cocaine to the tongue and mouth was inconclusive as there always seem to be taste fibres of the glossopharyngeal nerve which remain unanaesthetised (Fridberg, 1931). Reflexes from the stomach were excluded, since 40 ml. of 7 % ethyl alcohol, which is sufficient to stimulate the secretion of gastric juice, produced no response.

Cases have been described where the thought of food produced gustatory sweating showing that an afferent path from the higher centres might exist (Rappoport, 1920, cited by Fridberg), but this was not found to be so in the present case. The pathway is therefore considered to be by way of the taste fibres of the glossopharyngeal nerve and the chorda tympani component of the facial nerve (List and Peet, 1938).

Investigation of the Effector Mechanism.—As a first step in the investigation of the effector mechanism it was decided to try the effect of blocking the sympathetic nerve supply to the sweat glands of the face in various ways.

Effect of Supra-Orbital Nerve Block.—The left supra-orbital nerve was blocked at the supra-orbital notch by the injection of about 2 ml. of 1% procaine hydrochloride without adrenaline. An area of anaesthesia was produced in the distribution of the nerve and spontaneous sweating stopped in the anaesthetic area. No obvious flush was noticed in this area. Gustatory sweating tested after five minutes was found to be completely inhibited in the anaesthetic area. This indicates that gustatory sweating is a reflex via fibres present in the supra-orbital nerve and not the result of direct pharmacodynamic action on the sweat glands.

Effect of Cervical Sympathetic Block.—The left cervical sympathetic chain was blocked at the root of the neck by the injection of 20 ml. of 1% adrenaline free procaine hydrochloride. Spontaneous sweating stopped over the left half of the face and there was flushing of the area with a rise of skin temperature of 1·3°C. Gustatory sweating was tested after five minutes and there was no response. After 15 minutes minimal sweating reappeared on the left side presumably as the effect of the block wore off. This suggests that the fibres subserving the gustatory reflex arc are present in the cervical sympathetic chain and are therefore presumably sympathetic fibres.

Action of Atropine.—Atropine sulphate, gr. 1/100, was given subcutaneously. After 30 minutes the patient felt his mouth dry and had difficulty in accommodation. Spontaneous sweating stopped and the face became perfectly dry. Skin temperatures remained equal on both sides. Gustatory sweating was abolished as expected, since the nerves to the sweat glands are cholinergic and atropine acts by preventing the utilization of acetylcholine. Gustatory sweating therefore depends on the integrity of fibres present in the supra-orbital nerve and the cervical sympathetic chain, and is inhibited by atropine. There is no reason to suggest that these fibres are any other than the normal sweat fibres.

Action of Tetra-ethyl Ammonium Bromide.—Since tetra-ethyl ammonium bromide produces a block of preganglionic impulses at the sympathetic ganglia (Acheson and Moe, 1946) and so inhibits normal sweating it seemed reasonable to try its effect.

Tetra-ethyl ammonium bromide 0·5 g. in 5 ml. was given slowly intravenously. The patient complained of a metallic taste in the mouth, generalized flushing, tingling of the extremities, and slight headache. Spontaneous sweating stopped. After five minutes a gustatory stimulus was applied and in a further three minutes sweating became obvious over the gustatory sweating area and was of moderate degree. All subjective effects of the tetra-ethyl ammonium bromide disappeared after 18 minutes and sweating continued on the left side for about one hour. The gustatory sweating reflex was therefore not inhibited completely by the action of tetra-ethyl ammonium bromide. The reason for this is uncertain.

Demonstration of Other Sweating Abnormality.—The next step in the investigation was to see if any other abnormality of sweating could be demonstrated in the gustatory sweating area and so the effect of heat, parasympathomimetic drugs, and pilocarpine was observed.

Effect of Heat.—The patient was stripped, covered in a blanket, and placed in a heat cage with the face showing but protected from direct heat. Sweating began on the trunk and on the affected left side of the face after about six minutes. After 11 minutes sweating appeared on the right forehead and after 35 minutes was profuse over the entire body. The left side of the face always sweated more than the right side, even after a further half-hour of drenching sweat. There was thus an excessive response to heat on the affected side. It is interesting that a similar excessive response to heat was found in the patient with syringomyelia mentioned at the beginning of the article.

Action of Acetylcholine.—Acetylcholine, mg. 50 injected subcutaneously, produced slight sweating on the left side of the face noticeable in eight minutes and lasting for five to ten minutes. A substantially similar result was obtained with the injection of mg. 5 of mecholyl.

Action of Pilocarpine.—Pilocarpine nitrate, 1/12 gr., was injected subcutaneously. Sweating became noticeable in three minutes and was profuse in 15 minutes, lasting for more than an hour. The sweating was most marked on the left side of the face, being comparatively slight on the right side. There did not appear to be any flush, and skin temperatures remained equal on both sides.

The left side of the face appears to be more sensitive to the action of heat, acetylcholine, and pilocarpine than the right side. Whether it is the glands themselves or another part of the gustatory sweating reflex arc which are sensitive remains to be decided.

Since a sensitivity of some sort appeared to be present it was decided on empirical grounds to try the effect of an injection of histamine. This had interesting results.

Action of Histamine.—Histamine acid phosphate, mg. 0·5, was injected subcutaneously. Definite sweating of moderate degree and involving only the left side of the face appeared within seven minutes and remained for 27 minutes. There was no accompanying malaise and skin temperatures remained equal on both sides. As has already been mentioned histamine does not produce sweating except as a result of severe side effects from overdosage. In such a case sweating is generalized. Here sweating was definitely localized to the gustatory sweating area.

The action of histamine was found to be completely abolished by an injection of atropine, and by supra-orbital nerve block, and cervical sympathetic block. These facts, when taken in conjunction with the localization of its action, suggest that histamine plays a part in the gustatory reflex arc. If so, it must act by way of the normal sweat fibres to the face since its action is inhibited when they are blocked.

Effect of Antihistamine Drugs on Gustatory Sweating.—The effect of the antihistamine drugs on gustatory and heat sweating was next investigated.

In order that approximate comparisons of effect could be made the drugs were used in therapeutic doses. The parenteral route was chosen, though not usually the route of choice, so as to avoid the possibility of an unwanted gustatory response.

'Anthesan', 50 mg., was given by deep subcutaneous injection. After 15 minutes all spontaneous sweating stopped and a stimulus by eating was applied, but only very slight sweating over the left half of the face resulted showing that the gustatory sweating response was greatly inhibited, and it remained so for about two and a half hours.

When the observation was repeated with ' antistin ', mg. 50, no appreciable effect on gustatory sweating was noted.

' Benadryl ' was found to have an action intermediate between that of ' anthesan ' and ' antistin '.

The effect of these drugs in inhibiting gustatory sweating was thus in proportion to their relative antihistamine activity, ' anthesan ' having the greatest antihistamine effect and ' antistin ' the least (Graham, 1947). Spontaneous sweating probably stopped on account of the slight anti-acetylcholine effect of these drugs where ' antistin ' has a greater effect than ' anthesan '.

Effect of Antihistamine Drugs on Heat Sweating.—The drugs were given in the same dose and by the same route as above and heat sweating was carried out under the same conditions as described before.

' Anthesan ' was given, and after 15 minutes when spontaneous sweating had stopped, the heat cage was applied. The trunk became moist in 10 minutes but the face remained perfectly dry until, after 40 minutes, the left side began to sweat, followed by the right side seven minutes later. Sweating on the right side then overtook the left side in intensity and after 68 minutes sweating on the right side was more profuse than on the left.

When ' antistin ' was given the normal response to heat sweating was substantially unaffected. The left side sweated earlier than the right side and always more profusely.

Once again the action of ' benadryl ' was intermediate between that of ' anthesan ' and ' antistin ', sweating being almost equal on both sides at the end of an hour.

When the dose of ' benadryl ' was doubled, sweating on the left side was further inhibited so that for the first time sweating began on the right side and remained more profuse on that side throughout the test. These drugs therefore acted in proportion to their antihistamine effect on heat sweating but only produced an appreciable effect in the gustatory sweating area. The anti-acetylcholine effect of these drugs was insufficient to influence the right side to any appreciable extent and so may be considered to have had a negligible effect on the left side. The contention therefore is that the inhibition of heat sweating on that side may be considered as almost entirely due to antihistamine activity. The corollary to this proposition is that the greater part of the sweating which appears on the left half of the face in response to heat is in fact due to histamine activity.

Discussion

As has already been pointed out, in a normal individual histamine does not produce sweating unless as a result of side effects. Sweating cannot be produced in a normal or sympathectomized area of skin by local injection, nor does a normal or sympathectomized limb sweat when histamine is injected intra-arterially.

The notable features in this case are that histamine produced sweating at all and that this sweating was produced only in the gustatory sweating area. The accurate localization of the sweating suggests that histamine or a similar substance plays a part in the gustatory sweating reflex arc. A further feature in support of this argument is the finding that the antihistamine drugs inhibit gustatory sweating in proportion to their antihistamine activity.

A further point of interest is the inhibition of heat sweating, a sympathetic but cholinergic activity, by the antihistamine drugs. These drugs do have a slight anti-acetylcholine effect which has already been shown to be negligible. It is therefore argued that the inhibition of heat sweating on the left side of the face by the antihistamine drugs might be considered as almost entirely due to their antihistamine effect and that the explanation of the excessive response to heat on that side is that it is due to histamine activity.

Where and how does this histamine act? One hypothesis might run as follows (Wilson, 1950). The stimuli to generalized sweating are emotion or a rise in blood temperature acting on a centre in the brain. If a part of this centre were in a state of constant vasodilatation it might respond readily to stimuli which did not affect other parts of the centre. If this vasodilatation were reduced or abolished by antihistaminics the sweating response to heat and other forms of central stimulation in the corresponding skin areas would be diminished, as in fact they were. An injection of histamine would for a short time increase the vasodilatation and so might increase the sensitivity of the centre to subliminal stimuli, producing sweating in the affected region.

The mechanism of the transmission of afferent nerve impulses in the central nervous system is unknown, but since some nerves have been shown to yield moderate quantities of histamine on extraction (Von Euler, 1948), they may be histaminergic that is to say, producing histamine at their nerve endings. If the afferent taste fibres of the salivary reflex were histaminergic, then following very strong stimuli, there would be an overflow of histamine which would make the neighbouring sweat centres hyperactive. This might explain the phenomenon of normal facial sweating on eating very spicy foods. Abnormal gustatory sweating as described would then be explained by constant excessive production of histamine with chronic vasodilatation in a strictly localized part of the centre. No cause has been suggested, nor has any explanation been given as to how it is so strictly localized. It is also difficult to fit into this picture the failure of tetraethyl ammonium bromide to inhibit gustatory sweating.

On the other hand, suppose that due to an abnormality in the efferent fibres they became

sensitive to histamine. Since the action of histamine is abolished by cervical sympathetic block the abnormality would have to be in the preganglionic fibres or central to them. If the abnormality of the fibres was such that an abnormal substance was formed at the nerve endings when an impulse passed through them, then if this substance were histamine or similar to it and under these conditions produced an excessive response, the excessive sweating response to all forms of central stimulation would be explained.

If subliminal sweat impulses normally occur in response to food then gustatory sweating would be explained as occurring in response to the reinforcement of these normal impulses by the histamine-like substance.

The failure of tetra-ethyl ammonium bromide to inhibit gustatory sweating might then be explained as a failure to block an abnormal chemotransmitter, the histamine-like substance produced by the abnormal pre-ganglionic fibres. The effect of tetra-ethyl ammonium bromide on histamine sweating was not tried as it was felt that there was some risk to the patient involved in the fall of blood pressure.

The antihistamine drugs would inhibit all forms of sweating since they would inhibit this histamine-like chemotransmitter.

The pathology of this abnormality is again unknown. Perhaps some form of neuritis in the preganglionic sweat fibres would explain it. A similar neuritis in the patient with syringomyelia mentioned before would explain the similarity in the reactions to heat, acetylcholine, and pilocarpine in the two cases. In that case it might be explained as a response to the pressure produced by the cavitation of the cord peculiar to the disease. However, neuritis of various types usually results in a loss of function of the nerve rather than an increase, and the whole hypothesis is rendered even more unsatisfactory by the lack of evidence for the occurrence of histamine in efferent sympathetic fibres, or of its production by them.

It has not been forgotten that the afferent side of the reflex arc might be responsible for the syndrome but it is very difficult to test this assumption.

There are obviously great gaps in the reasoning of the explanations offered but they are intended to indicate a tentative line of thought and not to be cast-iron deductions. It is difficult in any other way to find an explanation for the actions of histamine and the antihistamine drugs which have been described.

I wish to express my thanks to Prof. C. F. W. Illingworth for the helpful advice and encouragement which he has given me, and to Prof. W. C. Wilson for his valuable criticisms and suggestions.

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SPINAL MENINGITIS DUE TO *ACTINOMYCES BOVIS* TREATED WITH PENICILLIN AND STREPTOMYCIN

BY

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The involvement of the central nervous system by actinomycosis is rare. Ford stated in 1937 : " There are 40 cases on record in which the nervous system has been invaded. All reported cases have been fatal ; no treatment is of any value ". Later Friedman and Levy (1937), in an extensive review of the literature, found 108 cases of actinomycotic involvement of the central nervous system. Treatment was symptomatic and the cases were " invariably fatal ". Eckhoff (1941) has added two further cases to the literature.

The advent of antibiotics has greatly changed the prognosis of all varieties of actinomycosis. Cures with penicillin were reported in 1944 by Christie and Garrod, Wollgast, Herrell, and by many others since then. However, none of these writers reported on the treatment of a case where the disease invaded the central nervous system, and it was not until 1948 that Jacobson and Cloward described the cure of a patient with actinomycotic meningitis with sulphonamides, penicillin and streptomycin. Schneider and Rand (1949) later reported the recovery of a patient with an actinomycotic brain abscess treated by complete excision and antibiotics.

Actinomycosis of the nervous system may arise in one of three ways : (1) primary, (2) by direct extension, and (3) by metastasis. Most authors think that " primary " cases are those in which the original focus is healed or has remained undiscovered, and Cope (1938) drew attention to six cases in which an actinomycoma was discovered in the third ventricle. By direct extension the organism travels from lesions in the air sinuses, ear, pharynx, face, and the jaws. Spread is along the connective tissue planes but may occur through the bone. By the third route, the metastatic, the organism most commonly reaches the nervous system through the blood stream from other foci in the body, especially the lungs.

Friedman and Levy stated that in the 108 cases collected by them the distribution of origins were metastatic (bloodborne) 63 cases, direct extension 23 cases, and primary 23 cases.

We report below a case of actinomycotic meningitis cured by antibiotics which is of particular interest, first, because the disease remained localized to the spinal meninges and, secondly, because it is probably of the primary type, no other focus having been discovered despite careful search.

Case History

V.R., a woman aged 26 years, attended the Dental Department with pain in the right ear and trismus. Caries of the right lower seventh and eighth teeth was found. She was referred to the Medical Out-Patient Department on March 15, 1950, with a history of two months' dyspnoea on exertion, but no other relevant symptoms. There was a history of pleurisy two years previously. Examination showed pallor of the mucous membranes. Blood pressure was 120/70 mm. Hg. The nails were flat, no glands were felt, and there were no other relevant physical signs. Haemoglobin was 50% (Haldane), the red cell count 3·92 million, the colour index 0·64.

The patient was admitted to hospital and the haemoglobin was found to have fallen to 40%. A fractional test meal showed a low acid curve ; there was no occult blood in the stools. She was transfused with 2 pints of blood, given iron by mouth, and the lower right seventh and eighth teeth were removed under endotracheal anaesthesia. The crowns were very carious but no sinuses were present and the sockets healed normally. She was discharged on April 15 when the haemoglobin was 80%

On April 23, 1950, the patient attended again complaining of severe pain in both buttocks and the back of the legs for the previous five days. There was tenderness over the right sciatic nerve only. A radiograph of the lumbar spine was normal. She was re-admitted on April 28 when the pain was more severe and was keeping her awake at night. In hospital the pain spread to the back and hypochondrium. The sedimentation rate on May 5 was 41 mm. in one hour, and on the following day she began to vomit and pain became severe in the neck and the whole of the spine ; neck rigidity and a positive Kernig sign developed. On May 11 there was

marked head retraction and opisthotonos but headache was only slight. The patient remained lucid but there was a rise of temperature and the blood white cell count was 28,000 per c.mm. with 89% of polymorphonuclears. Intramuscular injection of penicillin and streptomycin

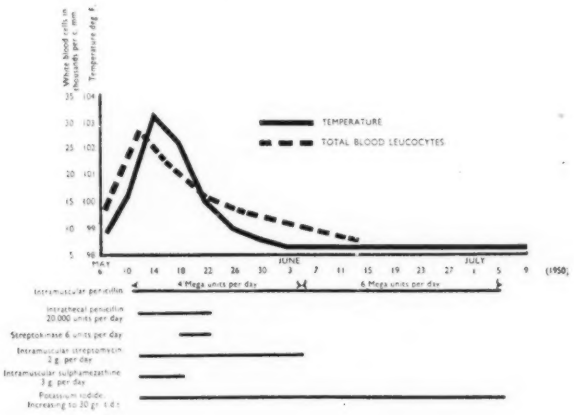

FIG. 1.—Chart showing response of temperature and leucocytes to treatment.

was begun (Fig. 1). On May 12, 5 ml. of thick pus was withdrawn at the third attempt to do a lumbar puncture. A stained film showed many pleomorphic Gram-positive filaments, some with clubbed ends (Fig. 2). A course of intrathecal penicillin was begun. A little more pus was withdrawn by lumbar puncture on May 13, but, although daily lumbar puncture was performed for eight days, no further fluid was obtained, so intrathecal therapy was abandoned on May 22.

From the beginning of treatment the temperature began to settle, while the neck rigidity and pain in the back lessened. A left external rectus palsy appeared on May 14, and lasted for eight days.

Following the onset of headache and mental confusion a trephine and right ventricular puncture was performed on June 2. The cerebrospinal fluid withdrawn showed 8 lymphocytes per c.mm. and 15 mg. of protein per 100 ml. Globulin was not increased. Chlorides were 720 mg. per 100 ml. Later there was urinary incontinence for seven to ten days but otherwise recovery was uninterrupted. A further attempt at lumbar puncture on June 16 again yielded no fluid, but cisternal puncture on June 22 yielded a practically normal cerebrospinal fluid (7 lymphocytes and 3 polymorphonuclears per ml.; protein 25 mg. per 100 ml.; sugar 60 mg.; and chlorides 730 mg. per 100 ml.).

The patient was discharged to a convalescent home on July 25, and attended as an out-patient on August 25 when, apart from slight neck rigidity, she was quite well. Radiographs of the spine, jaws, sacrum, skull, and chest taken in hospital had shown no disease.

Bacteriology.—Gram films of the original pus showed many pleomorphic Gram-positive filaments of varying length and staining, branching, and having many coccoid forms some with clubbed ends.

Aerobic cultures were all sterile. Anaerobic cultures in glucose broth produced granules, and visible small dry, white, wrinkled colonies were seen on glucose agar in four to five days. Glucose, maltose, mannite, saccharose, and lactose were fermented with the production of acid but not gas. A glucose broth culture was inoculated into four guinea-pigs which were killed at intervals of three to eight weeks. No disease was seen in any of the animals but it is known to be difficult to produce the disease in animals.

As a result of these reactions we concluded that the organism was *Actinomyces bovis*. It was completely inhibited by a penicillin concentration of 2 units per ml.

Discussion

The fact that 12 lumbar punctures yielded no cerebrospinal fluid, and pus on two occasions only, clearly indicates a complete spinal block.

It might be contended that the infection was entirely extradural, but it is unlikely that it could spread from the lumbar to the cervical region without any sign of extension outside the spinal canal.

FIG. 2.—Microphotograph of stained film of pus withdrawn from theca at lumbar puncture. × 800

Both the ventricular and cisternal fluids examined showed only a slight increase in cells indicating that the coagulative nature of the exudate was responsible for limiting this disease to the spinal leptomeninges. It must have reached the upper cervical region to have produced such marked head retraction. Here the present case differs from that of Jacobson and Cloward where the cranial cavity was also involved. The transient sixth nerve palsy in our case can be explained on mechanical grounds. It is not infrequently seen in the absence of infection, for example, after lumbar puncture.

Despite careful radiological examination no primary bony focus was discovered in either jaw or vertebrae. Nevertheless it is tempting to associate the dental extraction on April 5 with the onset of symptoms 18 days later. Is it possible that the organism was present in the mouth and reached the meninges by blood-borne embolism following the extraction? Okell and Elliott (1945) demonstrated that in no less than 75% of patients positive blood cultures were found a few minutes after dental extraction. These were usually *Str. viridans* but occasionally other mouth bacteria were isolated, and it seems reasonable to suggest that this was the portal of entry for the actinomyces. Mackie and McCartney (1945) state that " there is a considerable amount of evidence that the actinomyces sometimes occurs as a commensal in the mouth ".

Summary

The literature on actinomycotic meningitis is reviewed and a case of meningitis, limited to the spinal region, is described. It was treated and cured by penicillin and streptomycin.

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ELECTRICAL ACTIVITY OF THE HUMAN BRAIN DURING ARTIFICIAL SLEEP

2. REGIONAL DIFFERENTIATION OF RESPONSE TO BARBITURATE SEDATION

BY

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As Berger's (1933-36) original studies on the electrical activity of the brain were made with only two electrodes on the head, he was led to suppose that the brain functioned as a whole in this respect. This impression has persisted almost unchanged, except for sporadic attempts at more detailed analysis, and criticisms of this unitary theory have received little acceptance, especially in the field of human physiology.

In spite of Tönnies' (1933) early objections to Berger's conclusions, and the demonstration by Adrian and Matthews (1934) and Adrian and Yamagiwa (1935) of the special electrical characteristics of the occipital lobe, contemporary workers, for example, Foerster and Altenburger (1935), continued to support the unitary view. Then Rubin (1938) reported that the two cerebral hemispheres may beat asynchronously, and also that differences in the frequency of the resting rhythm may be observed between the anterior and posterior parts of the same hemisphere. At the same time Jasper and Andrews (1938) found that faster (beta) frequencies were more particularly associated with the frontal region.

More recent studies (Walter and Grey Walter, 1949; Hill, 1950a and b; Hill and Parr, 1950) indicate a possible relation between the temporal lobe and the production of slower (theta) frequencies, and between the frontal lobe and fast frequencies. Also to be considered from this point of view are studies on the maturation patterns of cerebral electrical activity in growing children (Lindsley, 1938; Smith, 1938, 1939, 1941; Barnes, 1946) which indicate that the acquirement of the adult pattern of brain rhythms is not a uniform process throughout the cerebral cortex.

Occasional studies on animals have also thrown the unitary concept into question, although the validity of some of the results reported remains in doubt. For example, Kornmüller (1933, 1935, 1937) claimed to recognize rhythms characteristic of various cytoarchitectural areas of the rabbit brain. Somewhat similar observations were made by Rheinberger and Jasper (1937) on anaesthetized cats, but the regional differences were not consistently apparent in unnarcotized animals. Clark and Ward (1945) also described area differences in the electrical activity of the cat's brain during the onset of natural or induced sleep. More recent studies (Swank and Foley, 1948; Swank, 1949; Swank and Cammermeyer, 1949; Garvin and Amador, 1949; Bailey, von Bonin, and McCulloch, 1949) indicate that regional differences may also be observed in dogs, monkeys, and chimpanzees during narcosis.

As no specific study along these lines is yet available for man, the opportunity has been taken, in the course of observations on the cyclical changes in brain potentials during barbiturate-induced sleep (Wyke, 1949, 1950b), to utilize a regionally distributed electrode pattern (Wyke, 1950a) for analysis of the cycle of changes in different areas of the human brain. It emerges that while only the crudest and most variable regional differences are apparent in the electrical activity of the waking human brain, serial recording during advancing barbiturate sedation discloses a course of events which appears to be individually characteristic for each of the major subdivisions of the brain surface. The method employed precludes any attempt at more precise anatomical correlation than this. Direct cortical and intra-cerebral recordings will have to be undertaken to determine whether architectonic correlations are justifiable.

Method

The material upon which this study is based consists of 100 subjects of all ages from infancy to late middle age, either clinically normal or else suffering from a variety of disorders of the nervous system. Studies made

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on the normal subjects were compared with those on patients with localized and non-localized cerebral lesions, and with those made on cases of psychiatric disorder.

This communication is concerned with normal responses. The variations seen in the different categories of abnormality will be discussed separately. Where possible several records were obtained on the subjects while awake, and in some instances two or three sleep records were made on separate occasions in order to check the consistency of response from time to time in the same subject.

Sleep was induced according to the method previously described (Wyke, 1949, 1950b), seconal sodium being administered orally in doses usually of 1·5 to 3 gr. (0·1 to 0·2 g.) for adults. Children received smaller doses by mouth or by rectum. Some subjects were given repeated small doses in order to induce a protracted onset of sleep (Wyke, 1950b), but no subject received more than 4·5 gr. (0·3 g.) as a total dose.

The technique of electrode placement is a critical factor in studies such as this, and the method, apparatus, and recording technique are described in detail in another communication (Wyke, 1950a). Using this technique, the activity of each major brain region has been studied at each stage of sleep in runs orientated in two planes at right angles to one another. The activity of each area is thus compared with that of adjacent regions, emphasis being placed on the differences between their patterns of electrical behaviour by virtue of the bipolar recording technique.

After initial trials with ear (or more remote) electrodes as reference points and of bipolar methods, the latter system was selected as giving a convenient and adequate representation of regional differences in electrical activity. However, ear leads (with the electrode inserted into the external auditory meatus) continued to be used as part of the longitudinal and transverse bipolar runs, and this arrangement proved to have special value for the examination of temporal lobe activity. The technical aspects of the bipolar method are fully discussed elsewhere (Grey Walter, 1938 ; Williams and Gibbs, 1939 ; Gibbs and Gibbs, 1941 ; Hill and Parr, 1950 ; Offner, 1950). Suffice it to say that this method tends to cancel out potential changes common to two electrodes linked together, thereby more or less isolating the differences in local activity existing beneath them, and in addition, a study of phase relations and focal activity becomes possible.

Results

The overall sequence of changes in human cerebral electrical activity induced by barbiturate sedation has already been described (Wyke, 1950b). In the course of that study it became apparent that the pattern of events differed in various regions of the brain, and the present paper describes the cycle of events in terms of the individual regions of the brain in which they occur. The classification of the stages of sleep is that given in the paper referred to above, in which the concomitant somatic changes are also discussed. Although the cycle is described here for each anatomical region in turn, it will of course be apparent that all regions transverse their particular sequence of changes simultaneously, and with a certain degree of overlap from region to region. The nomenclature of brain rhythms employed in this discussion follows that given by Hill and Parr (1950).

Frontal.—In the frontal lobes (Figs. 1, 5, and 7) the most obvious change is a steadily progressive shift down the beta frequency spectrum during the early stages of sleep. During stage 1 there is usually little alteration in activity in frontal leads, except perhaps a slight but gradually progressive increase in the voltage of the waking beta rhythm, when present. Throughout stage 2 this increase in amplitude becomes more pronounced, while towards the end of the period episodic slowing of the beta activity becomes apparent. This slowed beta (16 to 18 c/s) activity gradually occupies more and more of the frontal frequency spectrum as stage 3 begins, and as this period develops short spindles of 16 c/s waves form while the faster frequencies disappear. Towards the end of stage 3 further slowing to 14 c/s occurs, and this latter activity gradually increases in amplitude and amount as stage 4 begins, a change first apparent near the vertex.

During stage 4 almost steady firing of 14 c/s waves occurs in long spindles, of greatest amplitude near the midline, and at higher voltage in children than in adults. At the same time random slow (about 6 c/s) waves usually appear near the vertex, becoming more obvious as stage 5 begins, while the 14 c/s activity shows occasional slowing to 12 c/s, appearing first and remaining more apparent in inferior, rather than superior frontal regions.

As stage 5 develops, 14 c/s activity tends to disappear in the inferior frontal leads, leaving short spindles of 12 c/s waves interposed between irregular theta (4 to 6 c/s) waves. Near the midline low voltage runs of 14 c/s activity may persist even in deep sleep, but late in stage 5 the principal feature of frontal lobe activity is steady firing of slow (4 to 6 c/s) activity at varying amplitude, with occasional superimposition of 12 c/s activity. This slow activity may focus in one or other superior frontal region, the focus appearing as stage 4 passes into stage 5.

Until the end of stage 4 most activity is bilaterally synchronous in the two frontal lobes, but beyond this point more and more activity becomes asynchronous, until, in deep sleep, the two frontal regions seem to be functioning with almost complete electrical independence. Similar observations apply to other regions of the brain in this respect.

Precentral.—In the precentral (Figs. 2, 5, and 7) regions the initial change as sedation begins is the development of gradually increasing instability of the resting rhythm. This rhythm, in cases with occipital alpha frequencies in the upper limits of the alpha band, is often 1 to 1·5 cycles slower than the occipital rhythm, and its gradual loss of stability usually precedes similar changes in the posterior regions of the brain.

Sometimes frontal beta activity spreads back into the precentral regions as it increases in amplitude during the later part of stage 1 and throughout stage 2. In any case runs of 14 to 16 c/s activity rapidly build up in the precentral regions during stage 2, so that by the beginning of stage 3 high voltage (60 to 80 μV) spindles of 14 c/s activity become prominent, especially near the midline. In many cases this 14 c/s activity focuses in one or other superior precentral region at this stage, or occasionally in both superior precentral regions. Towards the end of stage 3 and in the early part of stage 4 this 14 c/s activity ceases to focus and then slows, at first at random and then in episodes of gradually increasing duration, to 12 c/s, appearing in short spindles near the vertex, and mixed with 14 c/s and 6 to 7 c/s waves in the inferior precentral regions.

By the end of stage 4, 14 c/s waves have almost disappeared, except for occasional random activity, and lower voltage 12 c/s activity dominates the whole region, mixed with 6 to 7 c/s waves which gradually spread upwards from the inferior precentral regions towards the vertex. During stage 5 this latter activity increases in voltage and slows further to 4 to 6 c/s, producing spindles of theta activity separated by short runs of 12 c/s (occasionally low 14 c/s activity) near the midline. These theta spindles at first are bilaterally synchronous, but as stage 5 develops this synchrony is gradually lost. In deepest sleep random waves at 3 c/s may appear in the precentral regions, usually in inferior rather than in superior leads and often focusing on one or other side. This change is accompanied by an increase in the duration of the theta spindles, which now show little bilateral synchrony. Little or no activity appears in the faster frequency bands in the deeper levels of stage 5.

Postcentral.—In the postcentral (Figs. 3, 5, and 7) and parietal areas the sequence of changes is intermediate between the precentral and occipital regions, but on the whole tends to conform to the pattern of the latter, rather than the former.

In stage 1 and during the early part of stage 2 little alteration can be seen, except some shortening in duration of the alpha spindles. As stage 2 develops the resting rhythm becomes unstable, and there is a fairly abrupt decrease in amplitude of all frequencies towards the end of this period. At the same time faster frequencies build up from the background of unstable alpha activity, so that 12 c/s and then 14 c/s waves appear—a picture the reverse of that in anterior leads. Thus a 10 c/s alpha rhythm in the waking record first becomes unstable, then decreases in voltage and finally gives place to 12 to 14 c/s activity. By the end of stage 3 14 c/s activity is firing bilaterally in long spindles, of higher amplitude near the midline than in more inferior regions.

As stage 4 is traversed this 14 c/s activity decreases in amplitude, while slower waves (at 4 to 6 c/s) make their appearance. These appear first at random and then in short runs, bilaterally synchronous and of increasing amplitude, as stage 5 begins. As this latter period evolves the faster frequencies become less prominent again, while the theta frequencies are more and more evident. In the deepest levels of sleep all that remains is a slow oscillation of the baseline interrupted by random 4 c/s waves and with a superimposed low voltage ripple occurring episodically at about 14 c/s.

Occipital.—It is in the occipital (Figs. 4, 5, and 7) and in the anterior temporal regions that the earliest electrical signs of barbiturate sedation are manifest. The initial change in the occipital lobes is a gradual shortening of the duration of the waking alpha spindles, or the appearance of spindling in those subjects whose waking records show an uninterrupted rhythm. This occurs early in stage 1, and in some subjects there may be, at the same time, an increase in amplitude of the spindled activity which is usually evanescent, but may sometimes persist into the early part of stage 3.

Early in stage 2 random slowing of the alpha rhythm begins, producing a picture of increasing instability of the basic rhythm. As this period passes the increasing intervals between the shortening alpha spindles (which remain for the present at the waking dominant frequency) are occupied by mixed frequencies in the lower limits of the alpha band. During stage 3 alpha spindling at the normal dominant frequency steadily diminishes, while the mixture of alpha frequencies between them comes to contain an increasing proportion of slower components (but still within the limits of the alpha band). In some subjects low voltage 14 c/s waves may be seen superimposed occasionally on the slower frequencies during this period. But by the early part of stage 4 most subjects show such activity, which, towards the end of this period, occurs in short runs between the slower frequencies.

As stage 4 ends alpha frequencies gradually disappear, being replaced at first by 6 c/s, and then 4 c/s waves occurring at random. In most subjects the activity near the midline tends to be slower than that in the inferior parieto-occipital regions. As stage 5 begins still slower frequencies (2 to 4 c/s) dominate the picture, while faster frequencies soon disappear. Finally the amplitude of all frequencies diminishes, and a slow periodic oscillation of the base line is disturbed only by random waves at 2 to 4 c/s as the deepest level of sleep is attained. In cases where an alpha focus is identifiable in the occipital lobes, such a focus disappears towards the end of stage 2 or the beginning of stage 3, and no focusing at any frequency is seen in the occipital regions thereafter until the cycle is reversed on waking.

Temporal.—Changes in the temporal (Figs. 2, 3, 6, and 7) lobes seem to usher in the cyclical changes of progressive barbiturate sedation. In most subjects the dominant frequency in this region is 1 to 1·5 c/s slower than that in the occipital leads, and this rapidly loses its stability quite early in stage 1. At the same time faster frequencies (within the beta band) are increased in amplitude. These rapidly slow towards the end of stage 1, so that by the beginning of stage 2 short runs of 16 c/s activity are apparent against the background of slower frequencies.

As stage 2 elapses spindles of 7 to 8 c/s activity develop in the anterior temporal regions, while the beta (mainly 16 c/s) spindles are further increased in amplitude. By the end of stage 2 these high voltage beta spindles are replaced by runs of 14 c/s activity which steadily increase in duration during stage 3, and usually focus in one or other fronto-temporal region. During this latter period 6 c/s waves appear, at first at random and then in bilaterally synchronous runs. Seen first in the anterior temporal regions, this theta activity spreads backwards into the temporo-parietal region, while the faster frequencies in the former areas decrease in amplitude.

By the time stage 4 is well established activity in the anterior temporal regions consists of a mixture of 5 to 7 c/s waves, interrupted by runs of lower voltage 14 c/s waves. As the rest of stage 4 elapses there is further slowing throughout the temporal lobes, the frequencies in the anterior temporal lobes being slower than those in the mid-temporal and temporo-parietal regions. At the same time the amplitude of these slow waves increases gradually, while the 14 c/s activity decreases in voltage and slows at times to 12 c/s.

By the beginning of stage 5 the dominant frequency in the temporal lobes is about 4 to 5 c/s, and the proportion of 4 c/s activity increases gradually thereafter, while faster frequencies fall off in amplitude until they are represented merely by a low voltage ripple at 12 to 14 c/s superimposed on the slow waves. As stage 5 is traversed slowing becomes more rapid posteriorly than in the anterior temporal regions, so that in deepest sleep the latter regions show only a low voltage oscillation of the baseline at 4 c/s with a superimposed ripple of 12 to 14 c/s waves on the slow waves, while the mid- and posterior temporal regions show higher voltage irregular discharges at 3 to 4 c/s. Thus in deep sleep the anterior temporal lobes never display the degree of slowing apparent more posteriorly, although in the earlier stages of sleep diminution of frequency is more rapid in the former than the latter regions.

Discussion

Studies of the cyclical changes in electrical activity in different areas of the brain induced by barbiturate narcosis make it apparent that the brain does not respond as a whole under such conditions. While the changes in each region are by no means independent of those in other areas, there is sufficient dissimilarity in the time course and pattern of response between the various areas to permit their individual identification at most stages of sedation. These observations apply to both natural and barbiturate-induced sleep, the similarity of which has been indicated before both in animals (Bremer, 1937 ; Clark and Ward, 1945) and man (Berger, 1931 ; Gibbs, Gibbs, and Lennox, 1937 ; Brazier, 1949 ; Wyke, 1950b).

Workers with various animal species have previously noted lack of uniformity in the cerebral electrical response to barbiturate sedation. Thus Clark and Ward (1945) described area differences in the electrical activity of the cat's brain, observing that these differences were more prominent and followed a specific sequence in each region during the onset of natural or induced sleep. Swank and Foley (1948) found that during progressive narcotization of dogs with sodium amytal and nembutal slowing and finally suppression of electrical activity was apparent in posterior regions before it appeared in precentral regions. More detailed area differentiation in dogs was reported by Swank and Watson (1949) in a comparative study of the effects of ether, pentothal, nembutal, and amytal, and Garvin and Amador (1949) found that significant area differences appeared in the macaque monkey during dial narcosis. The latter authors state that similar observations in chimpanzees under dial have been made by Bailey, von Bonin, and McCulloch (1949) and indicate that electrical activity is correlated with general brain regions and not with detailed

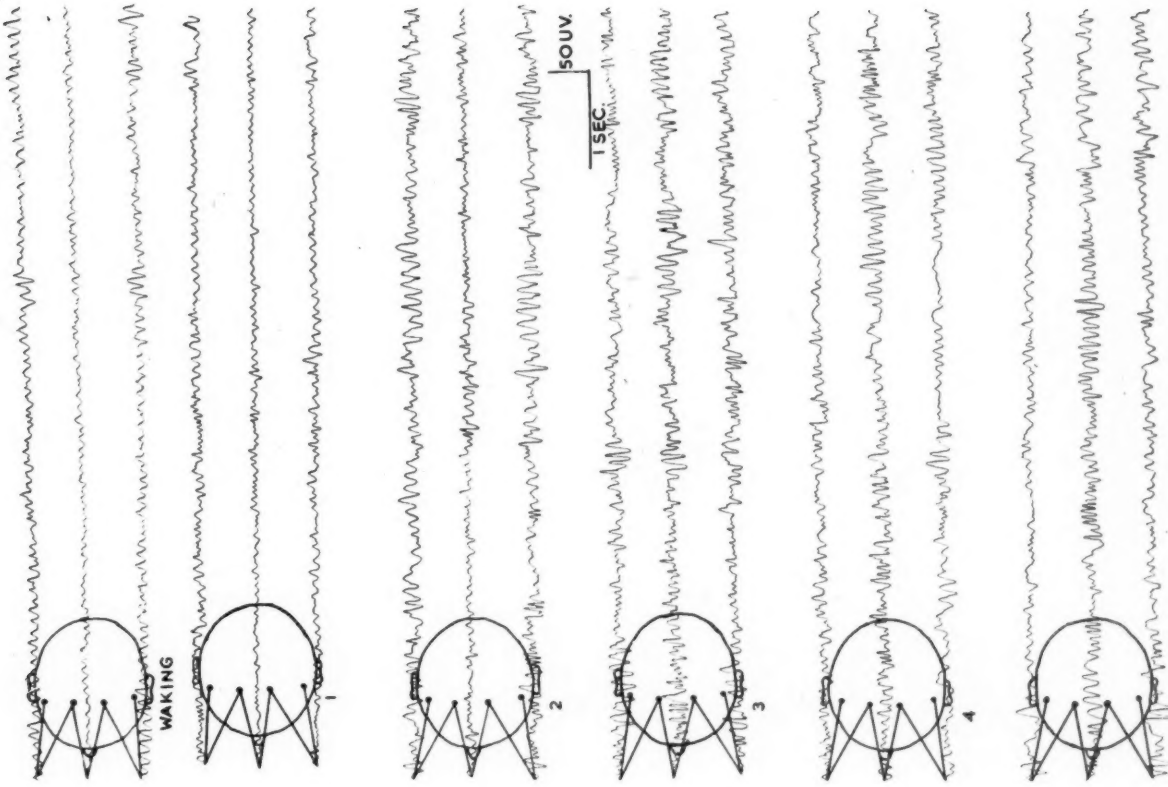

FIG. 2.

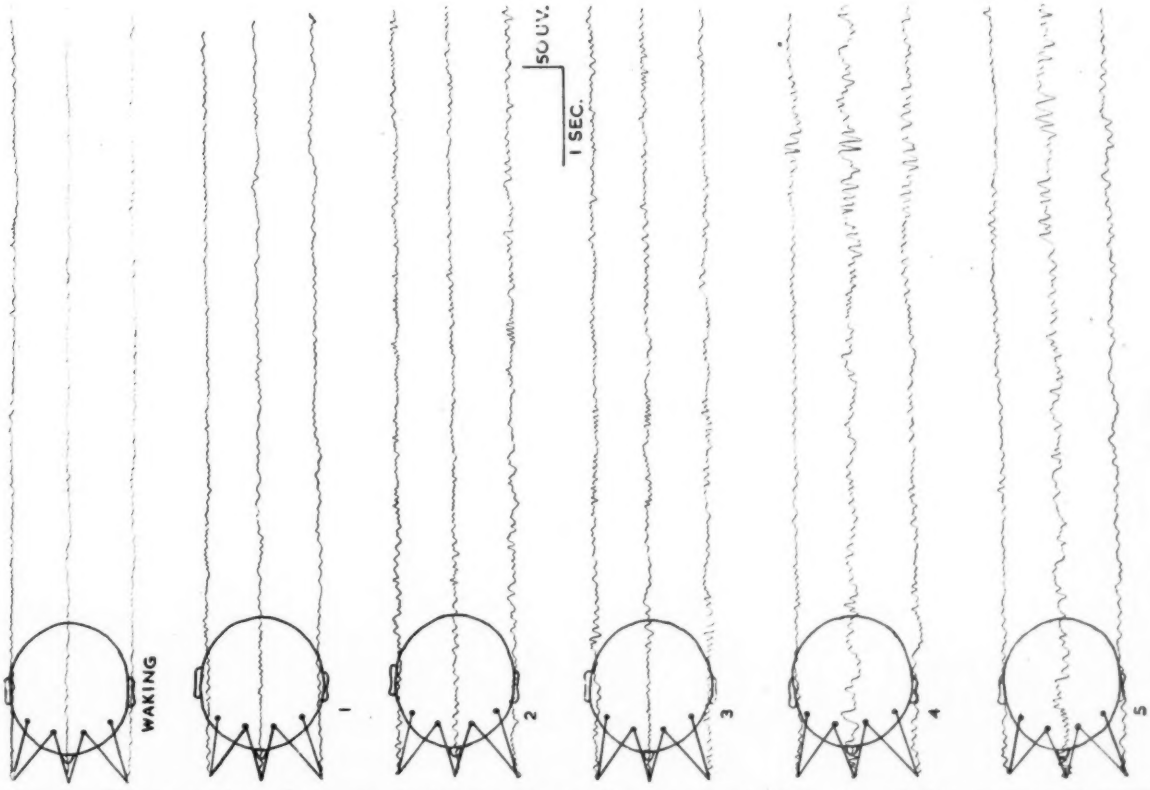

FIG. 1.

FIG. 1.—The succession of changes during the stages of progressive barbiturate sedation, as seen in transverse frontal leads. Figs. 1 to 4 are all from the same subject.

FIG. 2.—The succession of changes during the stages of progressive barbiturate sedation, as seen in transverse precentral leads.

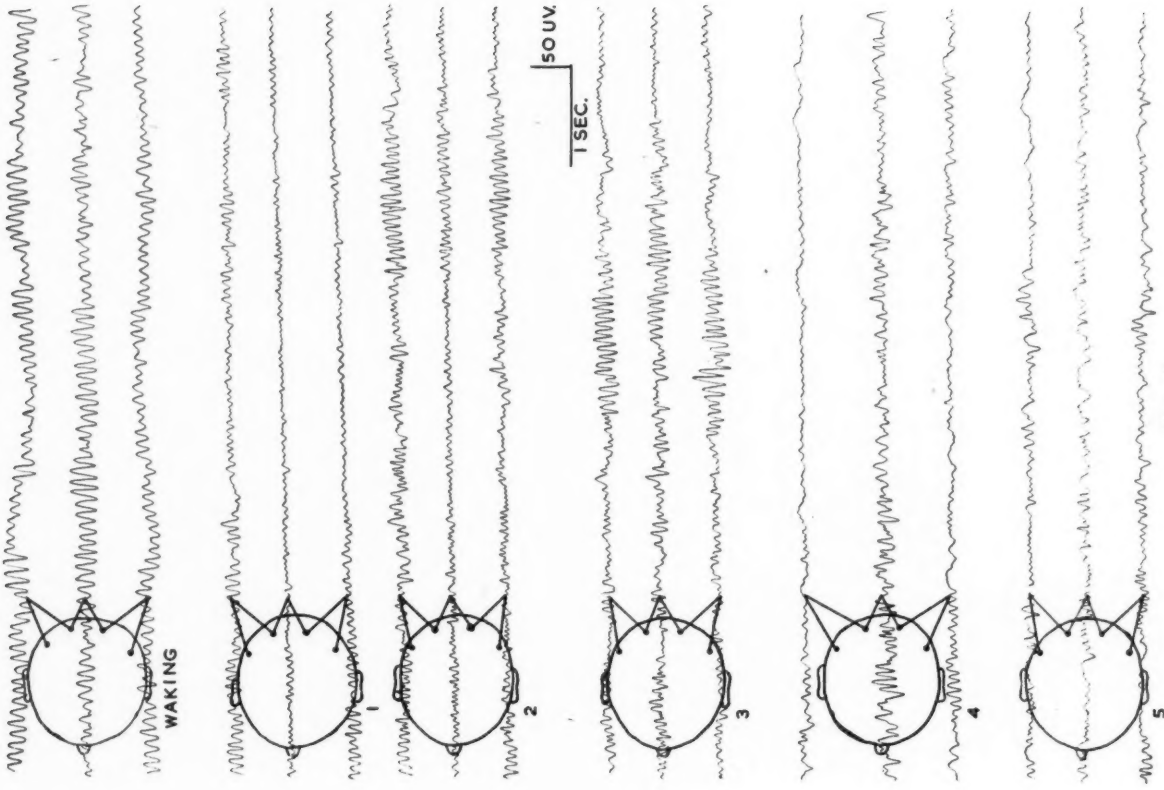

FIG. 4.

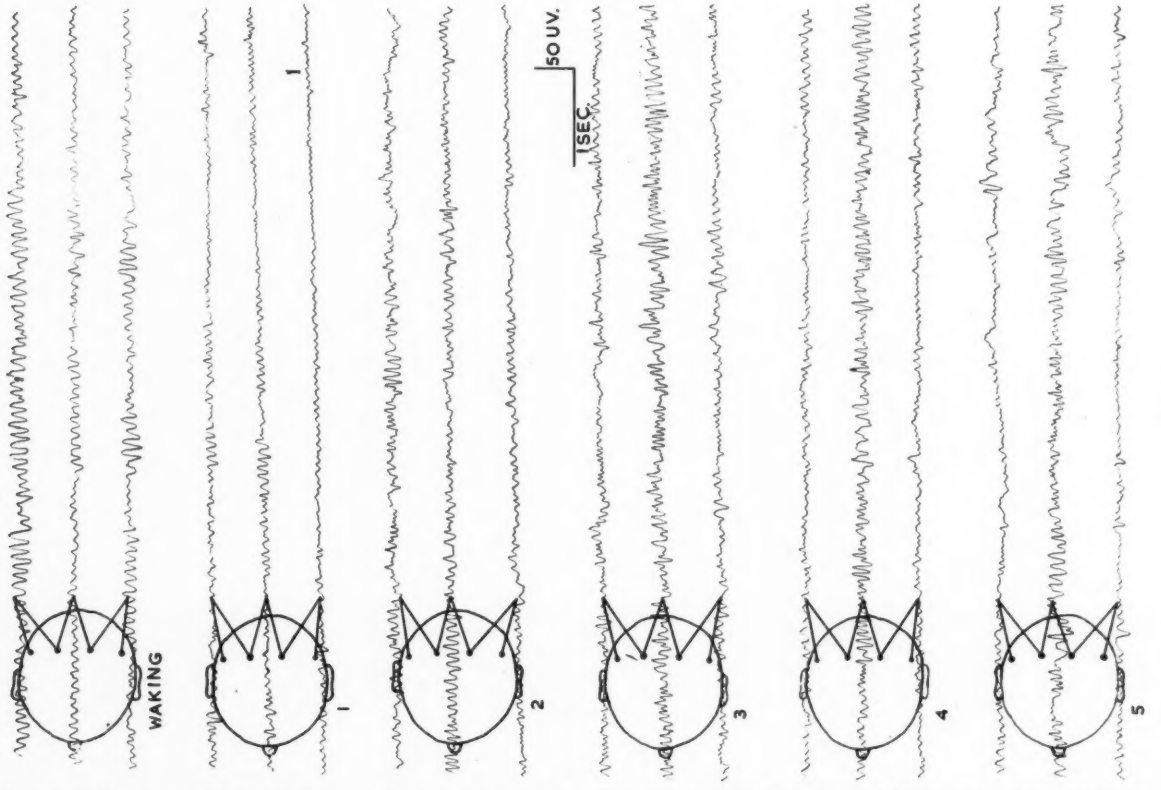

FIG. 3.

FIG. 3.—The succession of changes during the stages of progressive barbiturate sedation, as seen in transverse postcentral leads.

FIG. 4.—The succession of changes during the stages of progressive barbiturate sedation, as seen in transverse occipital leads.

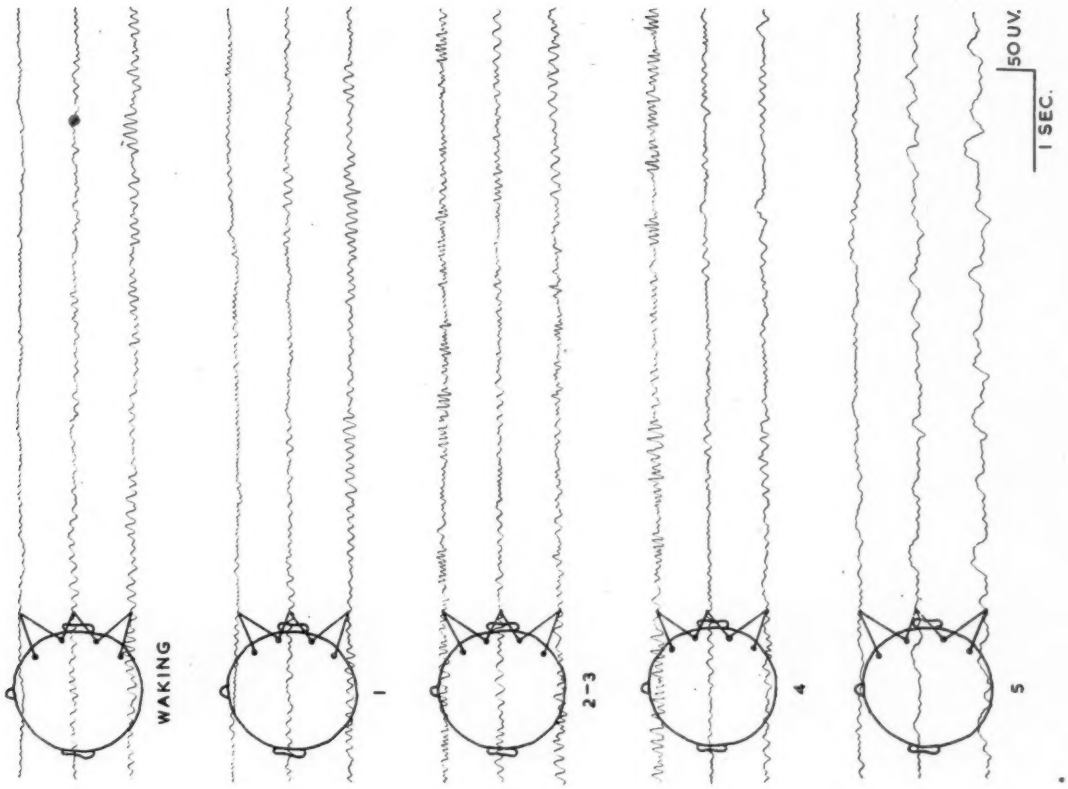

FIG. 6.

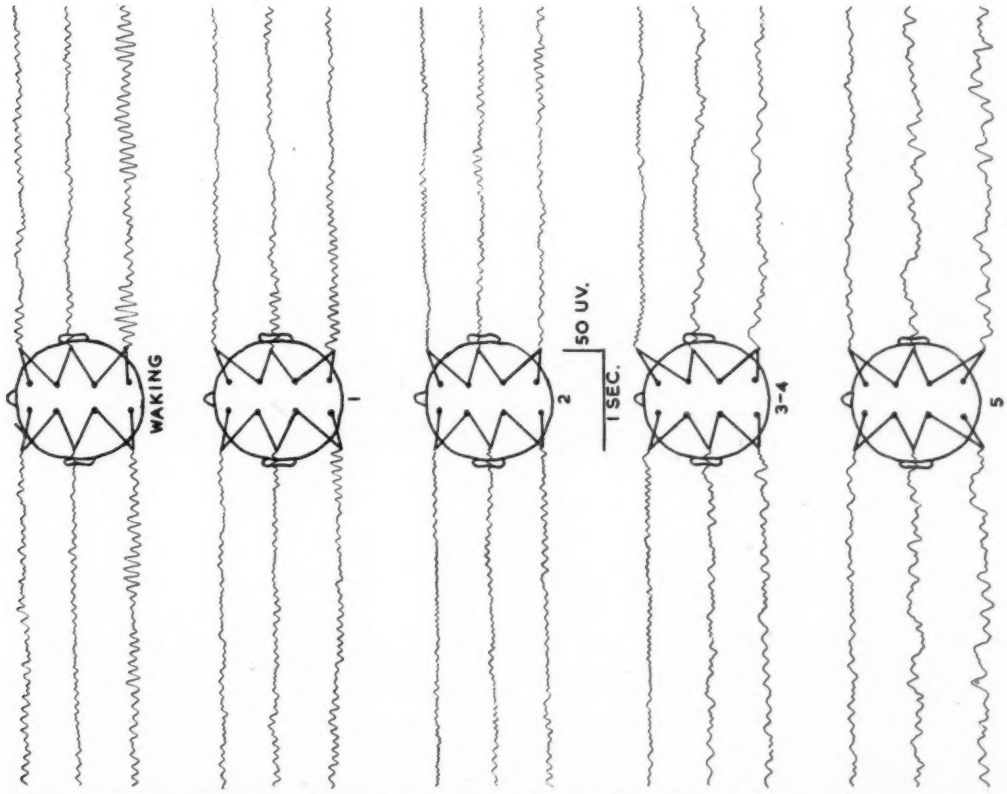

FIG. 5.

FIG. 5.—Representative stages in the cycle of progressive barbiturate sedation, as seen in parasagittal leads. Different subject from Figs. 1 to 4.

FIG. 6.—Representative stages in the cycle of progressive barbiturate sedation, as seen in longitudinal temporal leads. Different subject from Figs. 1 to 4 and 5.

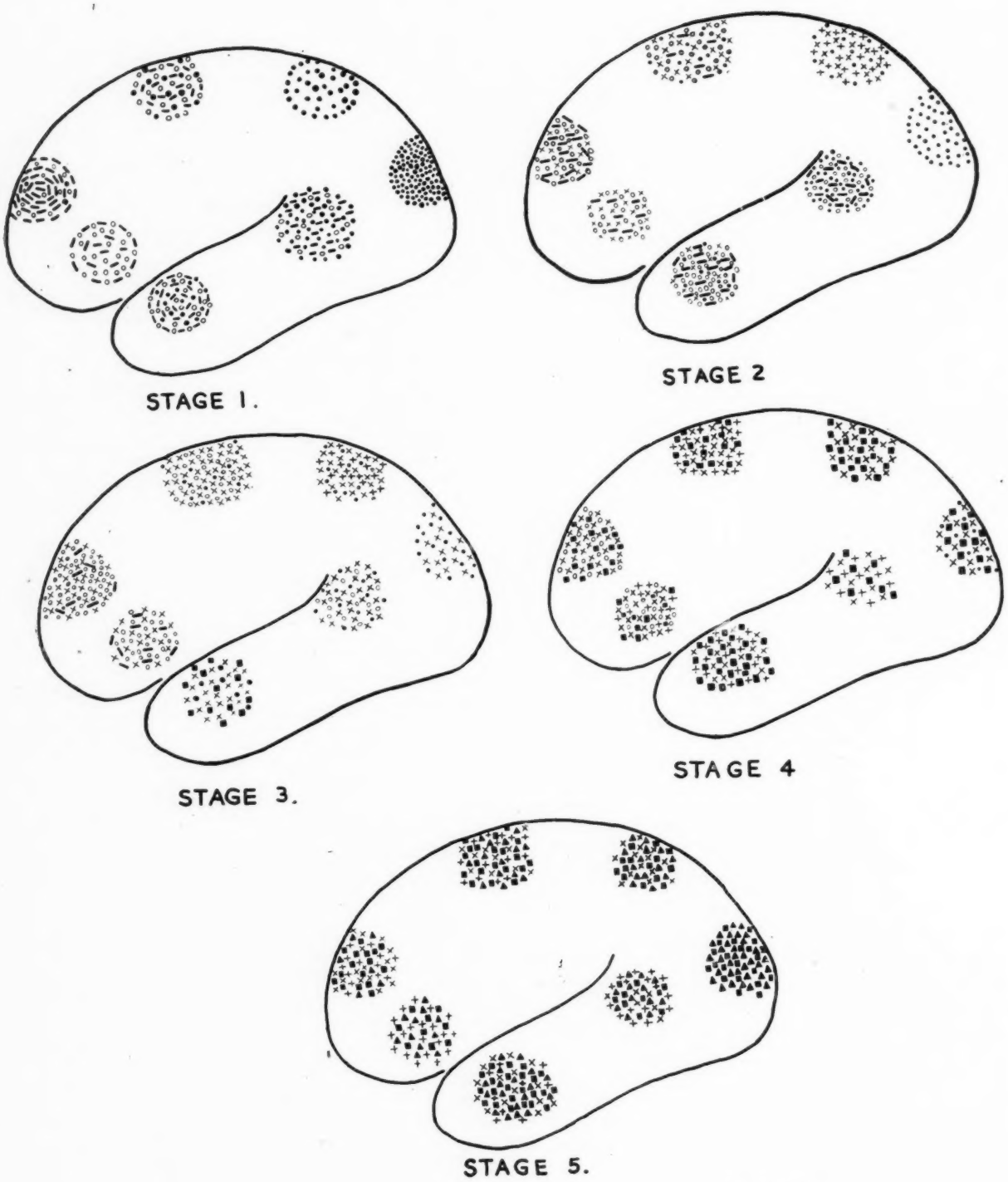

FIG. 7.—Diagrammatic representation of the frequency distribution in different regions of the brain during each of the stages of progressive barbiturate sedation. The various ratios were calculated on a percentage time basis.

cytoarchitectonic areas, as claimed by Kornmüller (1937). As their studies were not made during progressive narcosis, detailed comparison of their results with those reported here is not possible.

Detailed studies of the area differences in electrical activity during barbiturate narcosis in man have not previously been reported, although generalized analyses of the overall changes in cerebral electrical activity due to various barbiturates have been presented from time to time (Berger, 1931 ; Gibbs, Gibbs, and Lennox, 1937 ; Cohn and Katzenelbogen, 1942 ; Brazier and Finesinger, 1945 ; Lennox, 1946 ; Isbell, Altschul, Kornetsky, Eisenman, Flanary, and Fraser, 1950 ; Greville and Heppenstall, 1950). Brazier and Finesinger in the course of their study of the effects of intravenously injected barbiturates, noted that high voltage fast activity appeared in the frontal regions before becoming apparent elsewhere and that recovery of normal patterns occurred first in occipital leads and appeared more slowly in anterior leads. These observations are confirmed in the studies reported in this and the preceding paper. But the present experiments hardly support Brazier's contention that the fast frequencies constitute a " new " rhythm, suggesting rather that they are derived from the beta rhythm. Lennox and Coolidge (1949) made recordings from several areas of the head during injection of pentothal, but reported only on the distribution of 12 to 15 c/s activity. They suggested that 12 c/s runs during sleep appeared mainly in the frontal regions, while 14 to 15 c/s activity was more diffusely distributed but tended to be most prominent in the paracentral leads. The present findings agree with this in general, but emphasize that the frequency distribution depends on the stage of narcosis at which the electrical activity is sampled. At certain levels of sleep in all individuals 12 c/s activity is more prominent frontally, but it can be observed in paracentral and parietal regions at deeper levels. Similarly at some levels of narcosis 14 to 15 c/s may appear more prominently in paracentral regions, but at lighter levels it dominates the fronto-temporal discharge. At still deeper levels it may be more apparent in the occipital leads than elsewhere.

Again Brazier (1949) found that there was a shift of focus of maximum activity from the parieto-occipital regions to the frontal lobes during the passage from waking to sleep. Similar observations have been made in the present studies, which also confirm Brazier's identification of a precentral focus of 14 c/s spindles during the development of sleep. Detailed analysis indicates that the occipital focus is usually lost as stage 2 passes into stage 3, while the precentral focus of 14 c/s activity shows up as stage 3 develops. The latter focus varies in its actual site, but is usually somewhere in the fronto-temporal regions, and more often in the superior precentral region than elsewhere. As still deeper sleep supervenes these secondary precentral foci disappear, and a more rostral slow focus appears, so that in deepest sleep no focal activity is usually apparent in any area of the brain surface except the frontal regions.

The point to be emphasized, within certain limits, is that no one frequency is characteristic of any cerebral region at all stages of barbiturate-induced sleep, but that at any given level of narcosis the major cerebral areas differ from one another in their overall frequency spectrum. As the level of narcosis changes, the frequency patterns of the different cerebral areas change also, and the dominant frequency of one region may become dominant in another while disappearing in its original site. But the cycle of response occurs at different rates in the different cerebral areas, so that area differentiation at the various levels of narcosis depends upon differences in the time course of response in the various regional systems. This may be correlated with the progressive changes in behaviour and reflex response which are observed to be associated with the passage from one electrical pattern to another (Wyke, 1950b), and it is not until the deepest levels of narcosis are attained that the spontaneous electrical activity of the brain assumes a more or less uniform pattern and area differentiation melts away into the background of slow activity which characterizes all states of deep unconsciousness of whatever origin, and which shows little differentiation from one subject to another (c.f. Loomis, Harvey, and Hobart, 1938 ; Knott, Henry, and Hadley, 1939 ; Henry, 1941).

In short, as the brain falls asleep it does so piecemeal. The activity of the various projection systems is serially depressed in a manner which is reflected in the progressive changes in mental, sensori-motor and reflex behaviour which are observed clinically during the passage from normality to deepest unconsciousness and back again. The results of this investigation lend little support to the theory of depression of function of successively lower " levels " by barbiturates proposed by Etsten and Himwich (1946), which may also be criticized on other grounds (Swank and Cammermeyer 1949), or to the " deafferentiation " theory of Bremer (1935, 1937). Instead, the overall impression conveyed by the present studies corresponds more or less to the picture drawn by Sherrington (1940) in " Man on His Nature ". More detailed discussion of the possible mechanisms of these effects is reserved for a succeeding communication.

Summary

The cyclical changes induced in each of the major subdivisions of the human brain surface by progressive barbiturate sedation are described.

Evidence is presented to show that during the onset of sleep the brain does not respond in an overall uniform fashion.

It is suggested that while in the waking human brain different cortical areas do not usually possess well-defined electrical identities, during the onset of sleep they pass through a period when they may assume more or less independent patterns of electrical behaviour, the pattern of electrical activity at each stage of sleep being characteristic of the particular region.

I should like to thank Miss F. M. Taylor and Miss B. L. Thomas, B.Sc. for their assistance in this investigation.

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BOOK REVIEWS

Cerebral Angiography. By P. Almeida Lima. 1950. London : Oxford University Press. Illustrated. Pp. 221. Price 45*s*.

Cerebral angiography was developed in 1926 in the Portuguese school and has undergone rapid advances in recent years. It is appropriate that the first text appearing in this country should come from the pen of Professor Lima who with Egaz Moniz did so much of the pioneer work. The history of its development makes interesting reading. The first attempts at angiography in man were made by percutaneous puncture of the carotid artery, but this was discarded in favour of the surgical exposure of the vessel. The author still prefers this latter method and also emphasizes the advantages of using thorotrast but, as he himself points out in a footnote, this section on the technique was written in 1946. Since then the percutaneous method has been increasingly adopted and other substances such as diodone substituted for thorotrast. The advantages of antero-posterior angiograms as well as lateral views are also now well recognized, but these changes are to be expected in a subject which is being so actively explored and does not detract from the value of this important monograph.

The technique of injection is carefully described and this is followed by a description of the normal angiogram and a consideration of tumours in various sites. There is also a chapter on intracranial vascular lesions.

The illustrations, mainly of lateral angiograms, are excellent and their interpretation is assisted by several line drawings.

The book is a credit to both author and publisher, and in congratulating them on this work, we look forward to the next edition which will be required before long.

Introduction à la Psychochirurgie. By P. Puech, P. Guilly, and G. C. Lairy-Bounes. 1950. Paris : Masson & Cie. With 13 illustrations. Pp. 166. Price Fr. Fr. 520.

This short book represents the experience of the late Professor Puech and his collaborators in the neurosurgical service at the hospital of Sainte-Anne in Paris. It covers a wider field than the word psychosurgery commonly connotes in the American and English literature, where it usually refers specifically to operations on the frontal lobe and its connexions undertaken for the treatment of mental disease. The authors take as their subject all those intracranial surgical conditions which affect the psyche. This broader approach is already reflected amongst British neurosurgeons by the interest of Jefferson and Cairns in lesions of the hypothalamus, midbrain, and posterior fossa structures causing changes in consciousness, and in Penfield's work on the cortical localization of memory. The authors consider the subject under two headings : the surgery of recognizable cerebral lesions, tumours, trauma, cerebral oedema and upsets in cerebrospinal fluid dynamics—including intracranial hypotension—a subject to which the French school have given more attention than others ; and " functional " surgery consisting of frontal leucotomy and its derivatives. This approach will appeal to anyone with experience of the neurological practice of a large mental hospital where a cerebral tumour, not only of the frontal region, or other localized cerebral lesion, appears responsible occasionally for a florid mental abnormality, though the authors' experience of upsets in cerebrospinal fluid circulation as a determinant of mental deterioration seems to be happier than most workers in this country would yet admit. In their survey of leucotomy and its developments they make adequate mention of topectomy and thalamotomy and review the anatomical background. They also emphasize the importance of careful selection of cases for operation and of psychiatric rehabilitation afterwards. Full references are given, especially to the French literature.

Plasma Clot Suture of Peripheral Nerves and Nerve Roots. By I. M. Tarlov, M.D. 1950. Springfield, Ill. : Charles C. Thomas ; Oxford : Blackwell Scientific Publications Ltd. With 47 illustrations. Pp. 116. Price 40*s*.

The use of clotted plasma as a means of joining severed stumps of peripheral nerves is severely limited by the poor holding powers of the clot. In nearly all cases suture of peripheral nerves must be done with some tension and for this plasma clots are useless. Within these severe limitations, however, Professor Tarlov has shown that the method still has uses. He has made a careful study of the tensile strength and other physical properties of the clots and shown how to prepare an autologous plasma that sets up a minimum of reaction.

The situation in which the technique has hitherto been most useful has been in placing autografts of small nerves, for example, in the hand. These are difficult to insert properly with stitches and the use of plasma is a distinct advantage. The value of the method for placing cable autografts of larger nerves remains to be fully shown.

An interesting possible use suggested by Professor Tarlov is for the repair of anterior roots of the cauda equina, using posterior roots as autografts. He reports good innervation through such grafts in monkeys, but no functional recovery of the limb up to 26 months.

The use of plasma clots for surgery of human nerves is thus clearly a limited and specialized one, the procedure, however, that of choice for any very small

nerves to be sutured without tension. Although these conditions are rare in human surgery, they are frequent in experimental operations, and the use of plasma clots makes it possible to suture effectively many nerves of small animals that could not be properly joined with stitches.

Allgemeine und spezielle chirurgische Operationslehre. Vol. 2; by N. Guleke. 1950. Die Eingriffe am Gehirnschadel, Gehirn, an der Wirbelsaule und am Ruckenmark. Berlin: Springer-Verlag. 2nd ed. Illustrated. Pp. 589. Price DM. 126.

This second volume of Kirschner's system of operative surgery is devoted to the brain and spinal cord. The author, Professor N. Guleke, has clearly laboured without knowledge of neurosurgical advances outside Germany in the last 10 to 15 years, but in some respects it might be considered praiseworthy that he is able to produce this large volume in the face of such obvious difficulties. The book begins with a classic description of brain anatomy and cranio-cerebral topography on the lines of the earlier textbooks of this century. There follows a considerable section on the treatment of gunshot wounds which includes a description of sponge-tamponade in the treatment of penetrating missile wounds of the brain. In the treatment of meningitis urotropin receives a mention, but the author considers that sulphonamides are taking its place! Penicillin also is briefly referred to, but not other antibiotics. After a fairly complete description of ventriculography and encephalography, attributed to Dandy *and* Bingel, there is a brief reference to cerebral angiography.

Many methods of operating on tumours and other lesions in the different parts of the cranial cavity are described and profusely illustrated with rather mechanical and beautifully produced drawings which usually fail to convey any indication of the pathological changes actually encountered at operation, or of the more recent technical modifications which have so greatly improved the results of neurosurgeons. The chapters on the surgery of the cranial nerves are full and not without importance from the historical point of view.

Prof B. Brouwer: "In Memorial Volume." 1950. Amsterdam: F. van Rossen. With 300 text figures. Pp. 476. Price Fl. 11.85.

This tribute to Bernardus Brouwer (1881–1949) was planned by his colleagues some time before his unexpected death in November, 1949. It contains contributions from over 30 well-known neurologists from many countries, and also a record of Professor Brouwer's many important contributions to neurology.

Précis de Neurologie. With a Foreword by Prof. Forgue. By L. Rimbaud. 1950. Paris: G. Doin et Cie. 5th ed. With 280 illustrations, including colour plates. Pp. 1106. Price Fr. Fr. 3,500.

This is the fifth edition, extensively revised, of a work intended as a text for the pre-graduate student of medicine and as a brief reference book for the general practitioner and physician. It fulfils these functions well. To the English reader it has the additional advantage of exemplifying the approach to neurological problems made by the French school. This encourages one to reconsider the validity of clinical and physiological assumptions underlying neurological practice, as they often seem to differ from one country to another. The text is well balanced and contains an impressive amount of information in its 1,000 or so pages. Modern supplementary methods of diagnosis such as cerebral angiograms and electroencephalograms are discussed: but more recent findings in neuroanatomy and physiology, though briefly mentioned, are not as yet often incorporated into the interpretation of clinical findings. This book is so useful a compendium of clinical neurology that one wishes the author had given references to the literature: names are mentioned in the text but without references. It is illustrated by diagrams which are well reproduced and photographs which are not always so clear.

Einführung in die Neurologie. Bau und Leistung des Nervensystems unter normalen und pathologischen Bedingungen. By Oskar Gagel. 1949. Berlin: Springer-Verlag. With 172 illustrations. Pp. vii + 391. Price bound linen, DM. 30.60.

The general impression is that of a well-written and carefully illustrated book. The influence of Foerster on Gagel, one of his pupils and collaborators, can be clearly seen by the frequent use of Foerster's diagrams and the allusions to Foerster's work in the clinical descriptions. Although other authors are mentioned in the text, no further reference to their work regarding year or journal is made. To facilitate postgraduate studies it would be of great value to the students to have these references available. Like many other German post-war textbooks, the lack of recent knowledge of American literature is very striking, particularly in regard to recent advances in neurophysiology. Some minor criticism may be made about Figures 39a and b which are labelled as Nissl stains, but clearly they must be silver impregnations.

Apart from these shortcomings, the textbook should prove to be an excellent guide to the field of clinical neurology and neuropathology.

"Les Céphalees Vasculaires": Étude du Rôle des Vaisseaux cérébraux dans la Genèse des Céphalées. By Jacques Barbizet. 1950. Paris: G. Doin et Cie. Pp. 124. Price Fr. Fr. 500.

This book describes the part played by vascular disturbances in a large variety of headaches and facial pains, and especially in histamine headache and migraine. Observations on histamine headache, including study of the blood-meningeal barrier, lead the author to conclude that headache in this condition is due to cerebral oedema, not to arterial dilatation as such. No single physiopathological mechanism, he believes, will account for all the phenomena of migraine. In some cases there is vasoconstriction followed by vasodilation, in others cerebral oedema alone occurs, and it is important therapeutically to decide which mechanism is operative in a given case.

Physiologie et Biologie du Système Nerveux Végétatif au Service de la Chirurgie. By H. Laborit. 1950. Paris : G. Doin et Cie. Illustrated. Pp. 164. Price Fr. Ft. 620.

The author, a practising surgeon, disclaims any attempt to provide a comprehensive work on the vegetative nervous system, and states his aim as only to provide the surgeon with a few simply expressed ideas on the physiology and biology of the subject. The first section is anatomical and is mentioned as " très succincte ", but " trop " might be a more suitable adverb. The chemical mediators of autonomic action are next discussed rather more fully. Finally a third section, the longest, is devoted to the clinical applications of knowledge of autonomic function. This contains some of the findings and interpretations of the Tardieus and Reilly, who have worked extensively on the central representations of the autonomic. This work gathered together in a book, " Le Systeme Neuro-Végétatif ", by G. and C. Tardieu. Masson. Paris. 1948, reviewed in this journal, (**12**, 79), is not well known or much accepted in this country. The present small book represents a novel and on the whole unestablished approach to the clinical problems of the autonomic system. Its cursory treatment of the better-founded facts makes one doubtful of its authority for the more controversial.

Méthodes Biologiques en Clinique Psychiatrique. By Jean Delay. 1950. Paris : Masson et Cie. With 68 illustrations. Price Fr. Fr. 2,000.

This book by Professor Delay, one of the leaders of French psychiatry, demands attention as it gathers together his work on physical methods of treatment developed in various publications over the last decade. Although it comprises a wider view of the problems of psychiatry than the work by Professor Puech and his colleagues, the two books are to some extent complementary, as both give us the thought and practice of the Sainte-Anne clinic (see page 197). As the title implies, its approach to mental disease is essentially by way of the physiology of the brain.

In the first part electro- and air-encephalography are considered. This is mainly concerned with diagnosis, but the therapeutic effect of air injection is also mentioned in some detail. The author suggests that two factors may play a part in successful treatment—a relief of intracranial hypotension, and a stimulation of hypophyseal—diencephalic mechanisms, a type of " shock treatment," —from the air injection. Anything more than transient success here seems mostly in these cases with associated somatic endocrine abnormalities. The author claims that it is accompanied by biochemical and hormonal, as well as emotional and intellectual changes. He does not mention the possibility of temporary worsening of the mental condition, especially where dementia is present.

In the second part shock therapies and psychosurgery are dealt with in detail. The author's experience is in line with that of most other workers in this field. He points out that the indications, especially for psychosurgery, are at present symptomatic rather than nosological. The results are interpreted in terms of cerebral physiology and anatomy.

In the third and final section pharmacological methods are discussed. Psychosis associated with proven hormonal upsets, and " auto-intoxications " from liver or kidney dysfunction which (except in their acute forms) are looked at askance in this country, are mentioned with examples. Phenyl-pyruvate idiocy and alcoholic psychoses are also mentioned. Caspersson's work on the dinitriles is briefly discussed, and a claim is made for the use of glutamic acid in certain cases of oligophrenia, though this would seem from recent work to be doubtful. Various other drugs, penicillin in G.P.I., amphetamine, mescal and hashish, are also considered, and a long section on narco-analysis is included. This part of the book is discursive, but illustrates well Professor Delay's physiological approach to mental disease.

The book, as the viewpoint of an important section of French psychiatric opinion, will be of interest to psychiatrists and neurologists. The advantages of its physiological approach, which is widespread in psychiatry today, are clearly seen in the results of shock therapy and psychosurgery. Nevertheless, if these lead to complacency towards the problems of basic causes of mental disease, they may in the long run prove a stumbling-block to psychiatric advance.

Précis de Psychiatrie. By André Barbé. 1950. Paris : G. Doin et Cie. With 33 illustrations. Pp. 1116. Price Fr. Fr. 2,300, bound Fr. Fr. 2,700.

This volume is one of a series, the *Nouvelle Bibliothèque de l'Etudiant en Médecine*, and for the series as a whole the claim is made, no doubt with justice, that " elle renferme toutes les matières qui, au point de vue théorique et pratique, font l'objet de nos cinq examens de doctorat ". For both the students' purposes, the acquisition of practical knowledge and the study necessary to pass examinations, this sample of French teaching seems to the British reader to be unwarrantably rigid and formalized. In the first chapter, for instance, in which the presenting features of the patient are discussed, we find the dichotomy " facies sans expression " and " facies avec expression ", each of them associated with a separate list of maladies. The same system is followed throughout the book. The " folies raisonantes " are classified into persécutés-persécuteurs, quérulants, processifs ; persécutés mélancoliques et persécutés auto-accusateurs ; persécutés hypocondriaques ; persécutés mégalomanes ; persécutés jaloux ; persécutés érotiques ; persécutés religieux ; persécutés filiaux ; persécutés imaginatifs, persécutés séniles—each of these categories being accorded a separate clinical description. The " délires systématisés ", which include besides the " folies raisonnantes " also " psychose hallucinatoire chronique " and paranoia, are separated by the chapter on " états convulsifs (épilepsie, hystérie), from the " folies discordantes " to which they are clinically nearly allied.

Although markedly influenced by Kraepelinian nosology, the theoretical background is still mainly

that of the older French psychiatry. References in the text, which are very greatly too abundant, are almost exclusively to the French literature ; in the very short and inadequate section on leucotomy, for instance, there is no mention of the Anglo-American sources which are most important in this field.

French psychiatry, as is shown by the work of Delay, Ey and others, is capable of making as valuable contributions to the world literature in the present as it has in the past ; but it can hardly expect to develop its full stature until it has absorbed the lessons which have been learned in other lands.

Medizinische Psychologie. By Ernst Kretschmer. 1950. 10th ed. Stuttgart : Georg Thieme Verlag. With 23 illustrations. Pp. viii + 304. Price DM. 24.–.

The appearance of the tenth edition of this well-known work indicates the extent to which it is used in German-speaking countries as a textbook for medical students and for those who intend to specialize in neurology and psychiatry, and thereby emphasizes the gulf which now separates Germanic and Anglo-American schools. In this country or in the United States it would be unthinkable that a textbook of medical psychology should appear without a lengthy discussion of Freudian doctrine, and without an appreciation of the use and the value of tests and the contribution of psychometric psychology ; but it would be almost equally unlikely that such a textbook in these lands would make the same attempt to relate medical psychology with the basic sciences of physiology, biology, and neurology in one coherent and well integrated structure.

After a few pages of philosophical introduction, Kretschmer comes almost at once to grips with the anatomical and physiological basis of conscious behaviour. In successive chapters he deals with the inter-relations of cortex and brain-stem, endocrine system and total bodily habitus ; the functions of the thalamus and the control of affective changes ; the cortex and the significance of lesions causing apraxias, agnosias and dysmnesias, the frontal syndrome ; motor control and subcortical centres ; instinctive drives, affectivity, the mid-brain and the vegetative-endocrine system. Succeeding sections cover developmental psychology, sexual psychology and temperamental types, the personality and its reactions to the environment, with a final section on practical applications and psychotherapy. It will be observed that, though it is itself somewhat one-sided, this textbook would supply a much needed corrective to the one-sided approach to the teaching of medical psychology which is currently practised at our university centres.

The tenth edition of the book has involved much new writing, a good deal of use being made of the experimental work of Hess, and a considerable expansion of the discussion on the functions of the mid-brain. Electrophysiological work, which is adding considerably to our knowledge in this and other fields, does not receive due appreciation.

Modern Discoveries in Medical Psychology. By Clifford Allen. 1949. London : Macmillan and Co., Ltd. 2nd ed. Illustrated. Pp. 235. Price 12*s.* 6*d.*

This very readable book describes in a series of ten essays the development of medical psychology in recent times. Beginning with Mesmer, the author passes to Janet, Morton Prince, Freud, Adler, Jung, Kretschmer and Pavlov, to end up with Wagner-Jauregg and the physical methods of treatment of mental disorder. In the earlier essays, the style is so lucid and the language so untechnical that they might be enjoyed by interested readers without medical training. The same could hardly be said for the later chapters. Nevertheless medical students and general practitioners in search of a book on these subjects which is written in intelligible language and holds a fair balance between rival claims could read it with profit. The author is not entirely impartial, leaning indeed to the side of the Freudian orthodoxy, and it is probable that adherents of any one school would find his presentation of the views of that school inadequate. In the present state of dissension in psychiatry, however, it would hardly be possible to expect more. One small but irritating error might be corrected in further editions : the name of the Swiss psychiatrist was Bleuler and not Bleüler.

Das Autogene Training (Konzentrative Selbstentspannung). Versuch einer klinisch-praktischen Darstellung. By J. H. Schultz. 1950. Stuttgart : Georg Thieme Verlag. 6th ed. With 17 illustrations. Pp. 328. Price DM. 27.–.

The author outlines a method of progressive relaxation, akin to that advocated by Jacobsen, which he believes to be of value in the treatment of a variety of functional and psychosomatic conditions. Experimental observations on hypnotic and kindred phenomena which may be induced in states of relaxation are reported in some detail and followed by a lengthy theoretical discussion. Although relaxation therapy is clearly Dr. Schultz's hobby-horse, his book is written with considerable dignity and some regard for scientific standards of evidence. It will undoubtedly interest medical psychologists and others concerned with psychosomatic problems. At the same time, it is necessary to warn the prospective reader that many points of sound observation are embedded in a diffuse context of teutonic verbosity and that the author has not seen fit to append a summary of his argument and principal findings. It is therefore to be hoped that Dr. Schultz will consider contributing a short account of his methods and results to a British journal.

Klinische Psychologie. By Willy Hellpach, M.D., Ph.d. With chapters on **Klinische Psychologie des Kindesalters** by Bernard de Rudder, M.D., and **Klinische Möglichkeiten Experimenteller Psychodiagnostik** by Wilhelm Witte, Ph.D. 1949. 2nd ed. Stuttgart : Georg Thieme. Pp. 244. Price DM. 16.50.

Clinical psychology, as understood in this country, diverges in certain respects from what the Americans mean by it, but it is utterly different in both countries

from the subject dealt with in this book. Clinical psychology (referred to throughout, rather familiarly, as "klipsy") is concerned with "all kinds of mental conduct in bodily disorders": it has nothing to do with mental illness, and very little to do with the use of psychological procedures for investigating the diagnosis or causes of disease. Dr. Witte's chapter on psychodiagnostic methods suffers from lack of familiarity with the vigorous growth of this field of applied psychology in the English-speaking countries during the last decade. In the body of the book Professor Hellpach develops his concept of a series of "psychomas" that accompany physical states such as hunger, exhaustion, tuberculosis, typhoid, sepsis and all the rest. These psychomas are transient epiphenomena of the somatic process, he says. The notion is unacceptable, since, as expounded, it lacks precision and logical consistency. The book as a whole is idiosyncratic in language and outlook, and Professor Hellpach's rather eccentric standpoint is not likely to appeal to physicians.

The Inner Experience of a Psychoanalyst. By Theodor Reik. 1949. London: Allen & Unwin. Pp. 514. Price 21*s*.

The literary skill and the candour of this book, which is partly autobiographical, counteract the tedium induced by its lack of form. It is instructive to learn how Dr. Reik's mind works when he is psychoanalysing somebody: but we discover, as we read on, that some other psychoanalysts do it differently. He has large funds of disapproval for psychiatrists (he is a non-medical psychoanalyst) and is rather out of sympathy with many of the younger Freudians, especially when they use what he calls "psychoanalese" with slick assurance. His theme is the intuitive understanding, the native psychological perspicacity which the psychoanalyst should possess and constantly use if he is to be successful in his therapy: otherwise he becomes an "interpreting automaton". The book discloses a strongly marked personality and an artistic approach to the problem of human motives and conduct, incongruously allied with a tendency to anatomize and elaborate some rather simple matters (like the cartoon from *Punch* which is reproduced in Chapter XXIV). In contrast to many pretentious and stilted accounts of psychoanalytic procedure, this book discloses the inevitably personal, subjective and in many ways fortuitous character of the analyst's intervention.

Masochism in Modern Man. By Theodor Reik. 1949. Translated by Margaret H. Beigel and Gertrud M. Kurth. New York: Farrar Straus. London: Allen & Unwin. Pp. 439. Price 25*s*.

Dr. Reik, who is a slightly unconventional Freudian psychopathologist, asks himself why men sometimes strive for objects that entail physical and mental distress, voluntarily submitting to privations, sacrifices, and shame in spite of their customary avoidance of pain. Moralists and philosophers have tackled this problem before, but they have not related it so centrally to the sexual aberration called masochism. Dr. Reik arrives, after a lengthy and discursive journey through the problem, at the conclusion that the masochist aims at pleasure but is driven by anxiety and guilt to take up a defiant attitude, and so follows a perverse road to the attainment of his object. The book is a long essay in psychoanalytic speculation, and has no scientific pretensions

Von der Angst der Kranken. By Karl Scheele. 1949. Stuttgart: Georg Thieme Verlag. Pp. 76. Price DM 4.80.

Professor Scheele has written a series of 12 essays on the many ways in which patients can be affected by anxiety, and of the duties of the doctor in relation to them. Thus there are essays on the physiological effects of disagreeable emotions, on the anxiety the patient is likely to suffer during investigation, during treatment or before admission to hospital, at the prospect of disfigurement or maiming, the fear of death. The book is of general medical interest, and not specially noteworthy for the psychiatrist, but it is informed by a simple clarity and wisdom which should commend it.

A Miniature Textbook of Feeblemindedness. By Leo Kanner, M.D. 1949. New York: Child Care Publication. Pp. 33. Price $1.25.

This is a useful compendium for general readers. It contains a straightforward account of what mental deficiency is, illustrated by a few case-records, with notes on the genetic, cultural, material, physical, educational, and emotional determinants of the situation that physicians are confronted with in a mentally defective person brought to them for treatment or advice. Dr. Kanner pleads for invigoration and extension of the prevailing system for coping with mental deficiency in the United States.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Julius Wagner-Jauregg. Lebenserinnerungen. Herausgegeben und ergäntz. By L. Schönbauer and M. Jantsch. 1950. Vienna: Springer-Verlag. 46 text figures. Pp. 187. Price 17*s*. (bound 20*s*. 6*d*.).

Zur forensischen Psychiatrie "geistig gesunder" Hirnbeschädigter. (Beitrag zur Psychopathologie und Pathophysiologie der Ausnahmezustände. Fur Arzte und Juristen.) By Emil John, with a Foreword by Prof. Otto Pötzl. 1950. Vienna: Springer-Verlag. Pp. 96. Price 13*s*.

Hirnverletzungen. (Mechanismus, Spätkomplikationen, Funktionswandel.) By Walther Birkmayer. 1951. Vienna: Springer-Verlag. 54 text figures. Pp. 292. Price £2 11*s*. 6*d*.

Die Differentialdiagnose der Gehirngeschwülste durch die Arteriographie. By Doz. Dr. Mario Milletti. 1951. Vienna: Springer-Verlag. 54 radiographs and 3 text figures. Pp. 79. Price £2.

Recent Progress in Psychiatry. (The Journal of Mental Science, Vol. 2.) Edited by G. W. T. H. Fleming, in collaboration with Alexander Walk and P. K. McCowan. 1950. Pp. 711. Price 50*s*.

Pavlov : A Biography. By B. P. Babkin. 1951. London : Victor Gollancz Ltd. Pp. 364. Price 25*s*.

Psychiatric Aspects of Juvenile Delinquency. By L. Bovet. 1951. Geneva : World Health Organization. Pp. 90. Price 5*s*.

Technique of Psychoanalytic Therapy. By Sandor Lorand. 1951. London : George Allen & Unwin Ltd. Pp. 251. Price 12*s*. 6*d*.

Die Neurosen und die dynamische Psychologie. By Pierre Janet, with a Foreword by Robert Bing. 1951. Basel : Benno Schwabe & Co. Pp. 465. Price Sw. Frs. 32.–.

The Transmission of Nerve Impulses at Neuroeffector Junctions and Peripheral Synapses. By Arturo Rosenblueth. 1950. New York : John Wiley & Sons, Inc. ; London : Chapman & Hall, Ltd. 98 text figures. Pp. 325. Price 48*s*.

Atlas of Electroencephalography. By F. A. Gibbs and E. L. Gibbs. 1950. Massachusetts : Addison-Wesley Press. Illustrated. Pp. 324. Price $17.50.

Your Child Makes Sense. By Edith Buxbaum, with a Foreword by Anna Freud. 1951. London : George Allen & Unwin Ltd. Pp. 204. Price 12*s*. 6*d*.

The Day Hospital. An Experiment in Social Psychiatry and Syntho-Analytic Psychotherapy. By Joshua Bierer. 1951. London : H. K. Lewis & Co. Ltd. Pp. 56. Price 6*s*.

Incontinence in Old People. By John C. Brocklehurst, M.D., with a Foreword by Stanley Alstead. 1951. Edinburgh : E. & S. Livingstone Ltd. 62 text figures. Pp. 191. Price 30*s*.

Erkrankungen des Nervensystems. By Fritz Roeder. 1950. Göttingen : " Musterschmidt ", Wissenschaftlicher Verlag. 140 text figures. Pp. XX + 612. Price DM. 32.–.

Pathology of the Central Nervous System. A Study Based Upon a Survey of Lesions Found in a Series of Forty Thousand Autopsies. By Cyril B. Courville. 1950. 3rd ed. Mountain View (Calif.) : Pacific Press Publishing Association. 208 text figures. Pp. 473. Price $9.50 (plus tax where required).

Dementia Praecox or the Group of Schizophrenias. By Eugen Bleuler (translated by Joseph Zinkin), with a Foreword by Nolan D. C. Lewis. 1951. London : George Allen & Unwin Ltd. Pp. 548. Price 63*s*.

Modern Trends in Neurology. By Anthony Feiling. 1951. London : Butterworth & Co. (Publishers) Ltd. 202 text figures. Pp. 717. 63*s*.

The Neurologic Examination. Incorporating the Fundamentals of Neuroanatomy and Neurophysiology. By Russell N. Dejong. 1951. London : Cassell and Company Limited. 299 text figures. Pp. 1079. Price 110*s*.

Psychosomatics and Suggestion Therapy in Dentistry. By Jacob Stolzenberg. 1950. New York : The Philosophical Library, Inc. 5 illustrations, including 2 colour plates. Pp. 152. Price $3·75.

THE FEBRUARY (1951) ISSUE

The February (1951) issue contains the following papers :

The Projection of the Olfactory Epithelium on the Olfactory Bulb in the Rabbit. By W. E. Le Gros Clark.

Observations on the Passage of Weed's Prussian Blue Mixture along the Axis Cylinders and Inter-Fibre Fluid of Nerves. By E. J. Field.

A Method of Measuring Reflex Times Applied in Sciatica and Other Conditions due to Nerve-Root Compression By Donald S. Malcolm.

Arteriography and Carotid Artery Ligation in Intracranial Aneurysm and Vascular Malformation. By I. S. Wechsler, S. W. Gross, and Ira Cohen.

Disability Caused by Brain Wounds. By W. Ritchie Russell.

The Visual Field Defects in Subacute Combined Degeneration of the Spinal Cord. By G. H. H. Benham.

An Investigation into the Effects of Glutamic Acid on Human Intelligence. By J. R. Milliken and J. L. Standen.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1., price 7s. 6d.

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THE SURGICAL TREATMENT OF BLEEDING INTRACRANIAL ANEURYSMS*

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Since Symonds in 1923 and 1924 drew attention to the relationship between subarachnoid haemorrhage and leaking intracranial aneurysms, interest has been centred in the aetiology of this condition rather than in its treatment. Customarily spontaneous subarachnoid haemorrhage is treated by rest and quiet. Yet with such conservative management the mortality rate in most general hospitals ranges between 50 and 60%, while only 15 to 30% of sufferers make a satisfactory recovery (Table I). Spontaneous subarachnoid haemorrhage is thus a deadly and treacherous condition, and one which offers a challenge to surgery. Recently I (1950) drew attention to the possibilities of surgical treatment. In this particular paper I wish to consider in greater detail the operative management of leaking intracranial aneurysms, for these are lesions responsible for at least three-quarters of the cases of subarachnoid haemorrhage (Richardson and Hyland, 1941 ; Magee, 1943 ; also personal experience).

Several surgeons have reported their experiences with leaking intracranial aneurysms, but few have recorded more than two or three cases. Two main operative approaches have been tried—carotid ligation and a direct intracranial exposure of the aneurysm. Carotid ligation is efficacious when the aneurysm is situated on the internal carotid artery itself, but is of less certain value when the aneurysm is situated on the circle of Willis or on one of its distal branches, for it then becomes supplied with blood from the opposite carotid artery, and may once more cause symptoms. Furthermore, in cases of intracranial aneurysm

* Presented at the combined meeting of the Society of British Neurological Surgeons and the Sociedad Luso-Española de Neurocirurgia at Madrid on April 28, 1951.

where there has been recent subarachnoid bleeding, it would seem that carotid ligation carries an enhanced risk. Thus Schorstein (1940), in reporting the collective experience of the Society of British Neurological Surgeons, recorded five deaths in nine cases of bleeding aneurysm treated by carotid ligation (presumably internal carotid artery) as opposed to three deaths in 22 cases of aneurysm which did not bleed. Hermann, Obrador, and Dott (1937) recorded a 25% mortality rate in 12 cases of leaking aneurysm treated by internal carotid ligation, and Krayenbühl (1946) a 30% mortality rate in 20 cases. Rogers (1949), however, performed common carotid ligation in six cases with only one death.

An intracranial exposure of the aneurysm, although hazardous, permits of more precise treatment. The local measures available once the aneurysm has been exposed range from wrapping hammered muscles around it (Dott, 1933), to incising the aneurysm and packing muscle into its interior (McConnell, 1937), clipping the neck of the aneurysm (Dandy, 1938), trapping the aneurysm by occluding the artery on either side of its neck (Fincher, 1939), to shrivelling the aneurysmal sac with diathermy (Dandy, 1944). At least three cases are recorded in which the aneurysm has been excised (Cone, 1939 ; Dandy, 1944 ; Elvidge and Feindel, 1950). However, although the various surgeons listed above, and also Tönnis (1936), List and Hodges (1946), Jefferson (1947), Swain (1948), Murphy (1949), Elvidge and Feindel (1950), and Jaeger (1950), have each described cases treated by an intracranial attack, it is not yet possible to assess statistically the hazards of direct surgical intervention, because only Dandy and Jaeger have recorded more than an occasional case. Dandy (1944), encountered at operation 36 cases of aneurysm, 30 of which he treated by various local measures with nine deaths, but few of his cases were complicated by subarachnoid bleeding. Jaeger (1950) has recently reported 20 cases of leaking aneurysm situated on the intracranial internal carotid artery, which were submitted to a direct intracranial attack with five deaths.

It seems that most surgeons who have operated for intracranial aneurysm, either by carotid ligation or by a direct attack, have experienced mortality rates ranging from about 25 to 50%, and consequently have usually limited their interventions to patients gravely ill with recurrent bleeding, and considered past hope of spontaneous recovery. My own view, however, is that the prognosis of subarachnoid haemorrhage can be improved so much that all cases should be investigated and treated as a routine in a surgical manner.

CASE MATERIAL

This report is based mainly on 50 cases of leaking aneurysm operated on by myself or by my former associate, Mr. Anthony James, in the Neurosurgical Unit of the Dunedin Hospital, New Zealand, between May, 1946 and June, 1950. Both carotid ligature and an intracranial attack were employed, either singly or in combination. Many of the patients were gravely ill, and as a group they must be regarded as having a particularly serious outlook had they continued on conservative management. Of the 50 patients, 33 made good recoveries, eight recovered with an appreciable disability (total recovery rate, 82%) and only nine died (mortality rate, 18%). Twenty-four of the patients were 40 years of age or under, and of these only two died.

These 50 cases of leaking aneurysm were recognized as a result of arteriography or operation in 69 consecutive cases of recent subarachnoid haemorrhage admitted to the Neurosurgical Unit of the Dunedin Hospital from various hospitals in New Zealand. Half of these cases had experienced more than one attack of bleeding, and most were referred within less than a week of the last attack. The symptoms shown were similar to those usually reported in spontaneous subarachnoid haemorrhage. Arteriography was performed in all except the first two cases (both verified by operation), and at the time of this investigation the lumbar cerebrospinal fluid was still bloodstained or xanthochromic in all but seven cases. In only six cases was arteriography undertaken later than two weeks from the onset of the last attack of bleeding, for our policy was to perform this examination as soon as could be conveniently arranged after the patient's admission. The findings in the total group of 69 cases were as follows :—

	Cases
(A) Intracranial aneurysm (52 demonstrated examples)	50
(B) Arteriovenous malformations	4
(C) Intracerebral haemorrhage from a leaking artery without an aneurysm	1
(D) No lesion demonstrated	14
Total	69

In addition to the nine cases in Group A that died, two cases in the last group died and subsequently were examined at necropsy. All cases in Groups B and C, however, recovered after operation. The mortality rate for the whole series of 69 cases was therefore 16%.

Of the 50 cases, 22 were men and 28 women. Their ages ranged from 19 to 67 years, with three patients in the second decade of life, 10 in the third 11 in the fourth, 16 in the fifth, seven in the sixth

and three in the seventh decade. In three female cases subarachnoid bleeding was associated with pregnancy, and either preceded or followed an abortion or parturition by a few days; all three patients survived. Two cases were shown to have multiple aneurysms (two each, making 52 demonstrated aneurysms in 50 patients). The whole group of 50 cases can be conveniently divided according to the site of the bleeding aneurysm as follows :—

	Cases
Aneurysms of the intracranial portion of the internal carotid artery	19
Aneurysms at the bifurcation of the internal carotid artery (5 demonstrated aneurysms)	4
Aneurysms of the middle cerebral artery (11 demonstrated aneurysms)	10
Aneurysms of the anterior cerebral artery	17
(*a*) on proximal part of artery — 2 cases	
(*b*) in region of anterior communicating artery — 11 cases	
(*c*) on distal part of artery — 4 cases	
Total	50

PREOPERATIVE INVESTIGATIONS

In each case as full a neurological examination as possible was carried out, particular attention being paid to the presence or absence of a third cranial nerve palsy or of a subhyaloid retinal haemorrhage, for these were found to be important lateralizing signs. A hemiparesis, however, was of uncertain value, being sometimes on the same side and sometimes on the opposite side as the aneurysm, while inequalities of the pupils too were often misleading. (A detailed consideration of the neurological signs is outside the scope of this paper.) The diagnosis of subarachnoid haemorrhage was confirmed in all cases by lumbar puncture. In addition the Matas digital compression test and carotid arteriography were routine preliminary investigations.

Matas Carotid Compression Test

Dandy (1944) relied on the Matas carotid compression test for indicating the state of the collateral blood-flow from the opposite carotid artery through the circle of Willis, and he considered that, if a patient could withstand digital compression of a carotid artery in the neck for ten minutes, then the internal carotid artery on that side could be safely ligated without risk of hemiplegia. However, I have now seen several cases in which this test seemed to be borne well, but subsequently carotid ligation was not tolerated and the ligature had to be released. Probably the explanation is that it is difficult, if not virtually impossible, to make certain that the common carotid artery is completely occluded throughout the test. As a routine precaution we always have a second observer palpating the superficial temporal artery continuously to ensure that it does not pulsate while the examiner is compressing the carotid artery in the neck. Even this precaution is not sufficient, for we have noticed after partial ligations of the common carotid artery that the superficial temporal pulse may disappear, even though the common carotid artery is still partly open. Thus a negative Matas test must be accepted with reserve. A positive result, seen when digital compression of a carotid artery is not tolerated, certainly suggests an anomaly of the circle of Willis, and points to the need for caution in treatment.

Incidentally the Matas test may be of value in indicating the side of the aneurysm, for compression of the appropriate carotid artery will often ease the pain originating in an aneurysm.

Carotid Arteriography

The use of carotid arteriography in subarachnoid haemorrhage was pioneered by Moniz (1934), Dott (1933), and Jefferson (1937). In most of our cases the technique employed was that of Moniz (1933 and 1934). Under local analgesia each common carotid artery is exposed aseptically, while the patient lies in position on the radiographic table. Two small transverse incisions are made through the skin, one a little above the inner end of each clavicle, and access to the carotid sheath is obtained by separating the two heads of the sternomastoid muscle. The common carotid artery is then exposed by opening the carotid sheath and is often injected as it lies *in situ*. Sometimes, however, a tape is first placed in position around the artery to steady it. In either event 8 to 10 ml. of the contrast medium are injected at a time, and films are usually exposed for both the arterial and venous phases of filling. Each artery is usually injected twice, once for a lateral *x*-ray projection and once for an antero-posterior projection. At the conclusion of the radiological studies the common carotid artery is already exposed, ready for ligation, if this should be indicated.

The contrast medium generally used was 35% "diodone" compound solution, but in a few early cases "thorotrast" was used instead. Thorotrast gives clear-cut pictures with very little disturbance to the patient, but it is radioactive and is not excreted. Diodone solution gives almost as good visualization, and has the advantage that it is promptly excreted in the urine, but it may cause temporary spasm of cerebral vessels with the production of severe headache followed immediately by a transient hemiplegia. Often we

noted that the cerebral vessels close to an aneurysm might appear attenuated and somewhat irregular, and in the earlier stages of our experience we deduced this to be evidence of a local protective arterial spasm. We are not certain of this interpretation, however, since we performed arteriography with diodone solution and with thorotrast in a case on successive days, and observed arterial spasm with the first medium, whereas the vessels appeared entirely normal with the second. Undoubtedly diodone solutions themselves often cause spasm.

Dandy (1944) deprecated arteriography, mainly because of a fear of cerebral thromboses when thorotrast was used, and, if clinical features were present indicating the site of the aneurysm, he felt that the circle of Willis should be explored on that side without this diagnostic aid. Indeed in only four of Dandy's cases was arteriography performed, and then only because the examination had been made elsewhere before the patient was referred to Dandy. As might be expected, Dandy's records contain protocols of several cases of aneurysm, which had no localizing signs and were not located until they came to necropsy. Dandy, however, did concede that further experience might prove arteriography advisable as a routine procedure, because of the precise information it could give as to the site and size of the aneurysm, as well as to the patency of the collateral vessels. Moreover, we have not seen the thrombotic complications of thorotrast which Dandy feared.

There are several reasons why arteriography is desirable as a routine preliminary in the surgical investigation of subarachnoid haemorrhage. First, it is necessary to establish the nature, size, and site of a bleeding lesion—whether it is an aneurysm, arteriovenous malformation, vascular tumour, or other lesion—as often in subarachnoid haemorrhage there are no localizing or lateralizing neurological signs. Secondly, it may disclose that a massive intracerebral clot is present in addition to the subarachnoid haemorrhage, and an essential part of the operative management then is the prompt evacuation of the clot. Thirdly, arteriography may give information concerning the presence of anomalies in the circle of Willis and the state of the collateral circulation. A useful manoeuvre in testing the collateral circulation and in determining whether carotid ligation will prove efficacious, is to occlude temporarily one common carotid artery with a Crile's clamp and then inject the other with contrast medium. Finally arteriography may disclose the presence of two or more aneurysms in one patient ; this happened twice in my series.

Recently with increasing experience of percutaneous arteriography, we have resorted more and more to this method. But when the patient is gravely ill or has a stout neck and it is desirable to obviate any undue straining lest a recurrence of bleeding occur during the prodecure, we still prefer the " open " method of Moniz.

ELECTIVE SURGICAL PROCEDURES

If the aneurysm can be controlled surgically this seems an obvious advantage, and we have come to attempt surgical intervention in nearly all cases. Two different approaches can be used, carotid ligation and an intracranial exposure. They may be used either singly or together, and the choice in each case depends largely upon the situation of the aneurysm. Some general points will now be considered about each, before discussing their use according to the various sites at which an aneurysm may occur.

Carotid Ligation

Ligation of either the common or internal carotid artery was generally performed under local analgesia, a heavy silk ligature being drawn around the artery and tied with the vessel still in continuity. In our earlier cases each artery was tied tightly in a single stage, but in the later cases the common carotid artery was often tied in two or more stages. At the first stage the lumen of the artery was narrowed by a third or a half. Two or three days later the wound was reopened, and the artery occluded completely by a second ligature placed around it at the same level as the first. Our experience indicates that ligation of the common carotid artery in stages carries little risk of a subsequent hemiplegia (see later), and can be performed when a period of trial occlusion shows that a single-stage ligation of the artery would cause symptoms. Even the method of ligation recommended by Rogers (1944 and 1947), whereby the common carotid artery is tied tightly between ligatures and divided between them, is not without risks, and in the only cases in which we tried it, a case of aneurysm of the middle cerebral artery, a hemiplegia followed.

As regards exposure, the same Moniz approach employed for common carotid arteriography served also for ligation of that vessel. The internal carotid artery was always exposed by an oblique incision placed along the upper border of the sternomastoid muscle. At the first stage of ligation the adequacy of the collateral circulation through the circle of Willis was first tested by temporarily compressing the vessel with a Crile's clamp. If this compression was tolerated for a period of about half an hour, then the artery was usually tied forthwith. If,

however, the compression produced signs or symptoms of cerebral anoxaemia (and generally these appeared within a few minutes), then either the first stage of partial narrowing of the artery was proceeded with warily, or depending upon the situation of the aneurysm, an intracranial exposure would be undertaken without a preliminary carotid ligation.

We placed our chief reliance in avoiding a post-ligation hemiplegia upon this trial period of occlusion with a Crile's clamp. Also we often tested the adequacy of the collateral circulation by performing arteriography of the opposite carotid artery after the ipsilateral vessel had been occluded. In two instances in which a post-ligation hemiplegia appeared within a few hours of ligation, the neck wound was promptly reopened and the ligature released, with, however, recovery of the hemiplegia in only one case. We have not tried Rogers' (1944) method of simultaneously performing electro-encephalography during the trial period of compression of the common carotid artery and observing whether the normal cerebral rhythm persists or is altered by cerebral anoxia. In one of my recent cases this method had been tried in another hospital, where it was found that compression of the common carotid artery continued for only 50 seconds suppressed the cerebral rhythm. However, subsequently we were able to perform ligation of the artery successfully in two stages. Neither have we had personal experience of the method of Sweet, Sarnoff, and Bakay (1950) whereby the pressure within the distal part of the artery is measured and the effect of occlusion noted. This method probably merits further trials.

Operative Exposure of the Intracranial Internal Carotid Artery and its Branches

If need be it is possible to expose at operation not only the whole course of the intracranial internal carotid artery, but also a large part of the anterior and middle cerebral arteries as well. A unilateral frontal craniotomy of the type used for a " pituitary " exposure is turned on the appropriate side, usually under general anaesthesia (Fig. 1). When the anterior cerebral artery is to be exposed, the anterior limb of the bone flap should be fashioned so as to reveal 4 or 5 cm. of the superior longitudinal sinus immediately posterior to the frontal air sinuses, but in other cases the bone flap may fall a little short of the sinus. Next, in all cases, the lateral part of the dural envelope covering the frontal lobe is elevated off the orbital plate of the frontal bone, and is incised immediately in front of the sphenoidal ridge. As this is done, cerebrospinal fluid usually seeps through from the inner part of the Sylvian fissure, and, as the fluid is aspirated, the frontal lobe is raised off the anterior cranial fossa. Before long the optic nerve is exposed, and after the arachnoidal layer in front of this has been incised, cerebrospinal fluid flows more readily from the cisterns, thus facilitating the elevation of the brain from the base of the skull.

The intracranial portion of the internal carotid artery is located immediately behind and slightly lateral to the optic nerve (Fig. 2). To expose it properly the arachnoidal layer in front of it has to be incised upwards. Useful tools for this purpose are a fine-bore metal sucker to keep the field dry and a blunt neurosurgical hook with which to apply diathermy current to the various arachnoidal strands. Should small veins or even small arterial branches cross the line of the main artery or start bleeding, they can be caught in the mouth of the metal sucker and coagulated with diathermy. In this way the internal carotid artery is exposed to its bifurcation into the anterior and middle cerebral arteries, and this stage should be completed before the further exposure of the middle or anterior cerebral arteries is begun.

If the middle cerebral artery is to be exposed, the fissure of Sylvius must first be opened up (Fig. 3). To do this the arachnoidal layer covering the fissure must be divided, and then the opposing surfaces of the frontal and temporal opercula are gently separated. The most convenient place at which to start this process is on the convexity of the hemisphere just behind the Sylvian point, and from this spot the incision of the arachnoid is carried forwards to where the internal carotid artery has already been exposed. In my experience this incision has always run just above and parallel to the Sylvian veins, so that when the fissure is opened up these vessels are retracted downwards with the temporal lobe, and no sizeable vessels, apart from a few minute venous twigs which span the fissure, need be divided. The middle cerebral artery is located in the depth of the fissure, and can be followed forwards to its origin. If it has to be exposed in its more posterior course over the island of Reil, the arachnoidal incision over the Sylvian fissure has first to be extended backwards.

The exposure of the anterior cerebral artery is not difficult. In the first part of its course the artery passes inwards from the bifurcation above the optic nerve to the inferior aspect of the genu of the corpus callosum where it joins its fellow of the opposite side and the two are connected by the short anterior communicating artery. By elevating the inferior surface of the frontal lobe medial to the internal carotid artery, it is generally possible to

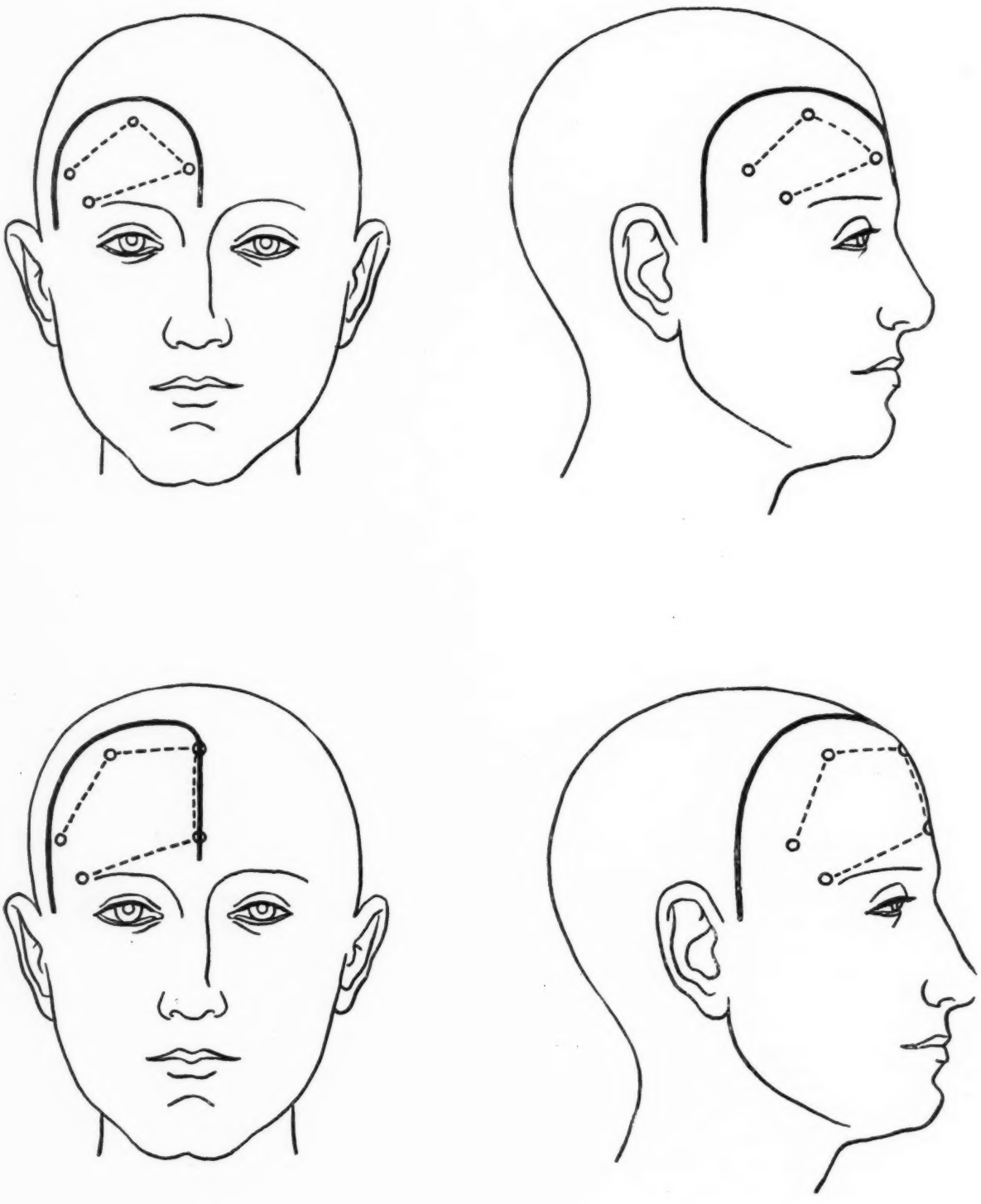


FIG. 1.—(Left) above, siting of scalp incision and of bone flap to expose intracranial internal carotid artery and middle cerebral artery. Below, sitings when anterior cerebral artery is to be exposed.

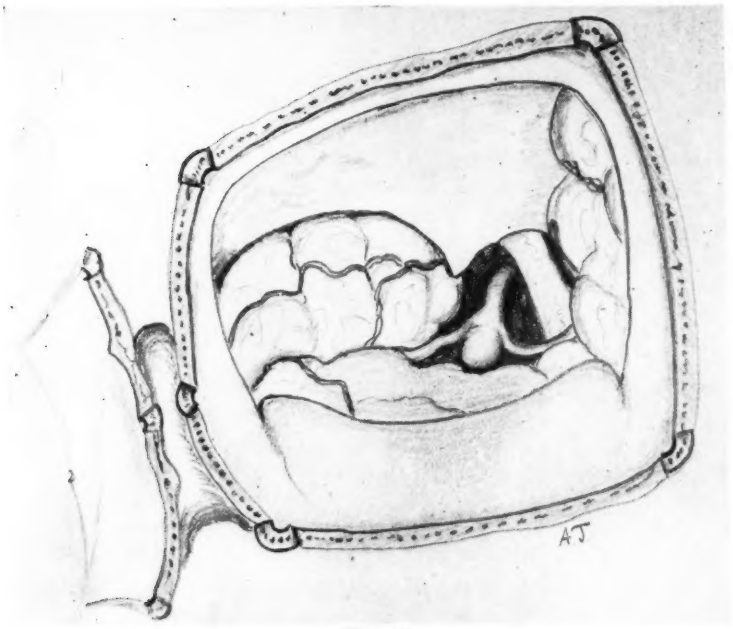


FIG. 2.—Operative sketch showing aneurysm at bifurcation of left internal carotid artery. Note relationship of internal carotid artery and its middle and anterior cerebral branches to the left optic nerve.

FIG. 3.—Operative sketch showing aneurysm of left middle cerebral artery displayed after the fissure of Sylvius has been opened up.

FIG. 2

expose the anterior cerebral artery as far as the anterior communicating artery, and sometimes even for a centimetre or so beyond this point to the summit of the genu. If the anterior cerebral artery has then to be followed further, the operative approach has to be changed from this subfrontal one to the superior one (Fig. 4). After any veins passing from the pole and superior margin of the frontal lobe to the superior longitudinal sinus have been divided, the mesial surface of the frontal lobe is retracted from off the falx and its fellow of the opposite side. In this way the two anterior cerebral arteries, right and left, are revealed as they run together over the corpus callosum.

Using these intracranial approaches it should be possible to expose practically every aneurysm on the intracranial course of the internal carotid artery or on its anterior and middle cerebral branches. As Richardson and Hyland (1941) and also Robertson (1949) have pointed out, many cases of aneurysm, particularly of the middle and anterior cerebral arteries, give rise to massive intracerebral haemorrhage within the adjacent parts of the brain in addition to subarachnoid haemorrhage. In such cases the brain may appear "tight" when the craniotomy flap is turned, and adequate exposure of the various main arteries is often not possible until the space-occupying lesion has been relieved by evacuation of the intracerebral clot. Many aneurysms, however, even when there has been recent subarachnoid bleeding, will not show any direct evidence of leaking when they are exposed. Occasionally, however, a little clot is seen alongside the aneurysm or perhaps some haemosiderin staining of the adjacent cortex, while sometimes the clot of an intramural haemorrhage can be seen in its wall. In five instances the aneurysm bled while it was under view, but only twice was the bleeding torrential. I have, however, not seen at operation

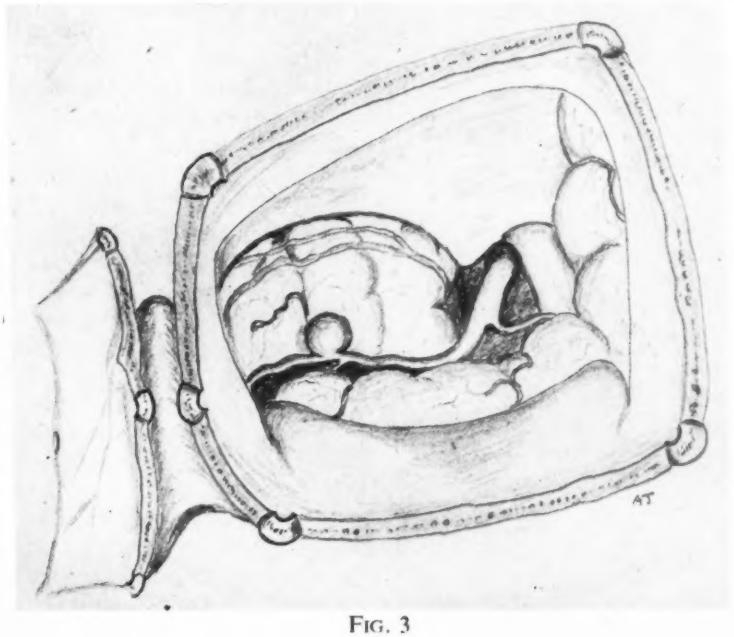


FIG. 3

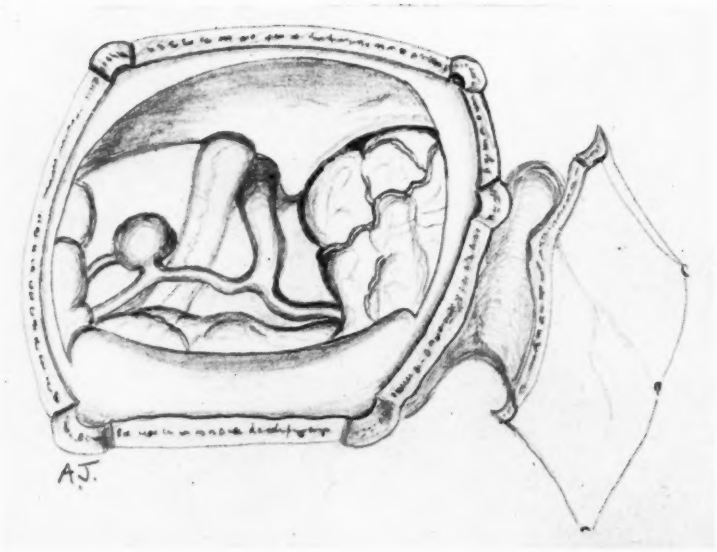


FIG. 4.—Operative sketch showing aneurysm of anterior communicating artery exposed by combination of subfrontal and vertical approaches from the right side.

the basal cisterns packed with solid clot as is so often seen at necropsy. Presumably subarachnoid clotting of such severity is a terminal phenomenon which causes death so rapidly that surgical intervention is precluded.

PROBLEMS WITH ANEURYSMS IN SPECIAL SITES

In the Intracranial Portion of the Internal Carotid Artery

This is one of the largest subgroups of intracranial aneurysms. There were 19 examples in our 50 patients, and they were treated surgically with 13 good recoveries, four recoveries with disability, and two deaths. Our experience indicates that, although carotid ligation is the sheet-anchor of treatment for this subgroup, wherever practicable this measure should be followed by an intracranial clipping of the internal carotid artery immediately above the aneurysm. Thus the aneurysm is "trapped" or permanently excluded from the circulation, as the remaining source of supply via the ophthalmic artery is of negligible importance.

Dott (1933) was the first to operate successfully on an aneurysm of this group, which he treated by wrapping with muscle. Subsequently his patient lived for 11 years without cerebral symptoms and then died of another cause (Dott, 1948). In 1939, Fincher reported the first successful trapping of an aneurysm in this situation, and since then both Dandy (1944) and Jaeger (1950) have added their experiences of the intracranial approach. Dandy operated on 13 cases with three deaths, but in only three of his cases had there been recent subarachnoid bleeding. On three occasions he clipped the neck of the aneurysmal sac, and in the remaining 10 cases he either trapped the aneurysm or coagulated with diathermy the portion of the internal carotid artery which bore it. Jaeger more recently has reported treating 20 cases by a direct attack with five deaths. In eight cases he clipped or ligated the neck of the aneurysm; in eight cases he trapped the aneurysm; and in two cases he wrapped it with a layer of "cotton". Other surgeons have treated these aneurysms, particularly by carotid ligation, but it is difficult to tell from their publications the numbers of cases treated and the results.

Aneurysms in this particular situation have certain characteristic arteriographic and clinical features. Almost always they arise either just above or just below the posterior communicating artery in the angle between that artery and the parent internal carotid artery. Consequently, in the arteriograms they are seen to project posteriorly or postero-laterally from the internal carotid artery, and are displayed to best advantage in the lateral arteriograms, whereas in antero-posterior views they may be superimposed on the carotid siphon (Figs. 5–9). Some writers have interpreted the arteriographic appearances as those of an aneurysm of the posterior communicating artery, but Dandy was insistent from his post-mortem observations that they are really aneurysms of the internal carotid artery. From the clinical viewpoint these aneurysms are immediately above the third cranial nerve where it passes forwards over the small triangular area of dura immediately lateral to the clinoid processes, and consequently a third cranial nerve palsy is a common feature (Albright, 1929; Jefferson, 1947). Indeed a third cranial nerve

palsy, either partial or complete, was noted in 13 of our 19 cases.

Experiences with Primary Internal Carotid Ligation.—Being on the internal carotid artery a few millimetres or more below the circle of Willis, these aneurysms are readily treated by carotid ligation. Several methods of carotid ligation were tried before stage-ligation of the common carotid artery, followed later by ligation of the internal carotid artery, was adopted as the routine sequence. At first, primary ligation of the internal carotid artery was tried and was carried out in eight patients, including one who had been first explored intracranially. In seven patients the artery was tied tightly in a single stage, and in the remaining one the artery was only partially occluded. The case that had been explored intracranially died, but the remaining seven survived, although three were left with a persistent hemiplegia. Of the four cases that made excellent recoveries, one on admission was blind with bilateral subhyaloid ocular haemorrhage, and subsequently after weeks of blindness his vision recovered completely.

In the first of the three patients who survived with a persistent hemiplegia, the weakness appeared rapidly on the third post-operative day in a man of 67 years, who had been given prophylactic heparin therapy in the first 36 hours. In the second, a young woman aged 19 years, intracranial bleeding recurred immediately following arteriography and caused rapid loss of consciousness ; carotid ligation was carried out within a few minutes and hemiplegia was noticed within a few hours. In the third case, a woman of 47 years, whose artery was only partially occluded, the hemiplegia appeared within eight hours and was not relieved by prompt removal of the ligature ; indeed when the ligature was released the artery, judging from palpation, was already thrombosed.

In the case which died (the second patient in the series on whom no preliminary arteriography was performed) the aneurysm was first explored intracranially and, when it was actually being exposed, it burst, resulting in a torrential haemorrhage which was controlled with difficulty by packing hammered muscle around the aneurysm. After shock from blood loss had been corrected by blood transfusion, the internal carotid artery was ligated in the neck. On the fourth day a contralateral hemiplegia appeared and the patient became unrousable. Death occurred on the eighth day, and at necropsy the internal carotid artery was found to be thrombosed up to the bifurcation, while extensive infarction had occurred in the brain in the territory supplied by the middle cerebral artery.

We concluded from this and from the other three cases that developed hemiplegia, that primary ligation of the internal carotid artery involves considerable risk of persistent hemiplegia developing, as has been stressed on a number of occasions by Rogers (1947 and 1949). The hemiplegia particularly affects the face and arm, the leg tending to escape. Subsequently we tried to avoid this complication by first ligating the common carotid artery, followed later by ligation of the internal carotid artery.

Experiences with Primary Common Carotid Ligation.—In our earlier cases the internal carotid artery was exposed for arteriography, and consequently this artery was then chosen for ligation. However, when the Moniz approach was adopted the common carotid artery became readily available instead. In two or three cases we found occluding the common carotid artery with a Crile's clamp preparatory to ligation produced cerebral anoxia signs within a few minutes. These signs, however, did not occur when the artery was only partially narrowed. It was from such cases that we came to develop the method of stage-ligation of the common carotid artery.

The technique of stage-ligation has already been described. Ten patients were treated in this way without any untoward complications (although one of the ten subsequently developed a delayed hemiplegia following intracranial tapping). Included in these ten patients were two who did not stand the trial occlusion of the common carotid artery with a Crile's clamp, yet they both tolerated partial narrowing progressing to complete occlusion in three stages. An eleventh patient (the remaining patient intended for treatment by stage-ligation) died two days after the first stage of only partial occlusion of the artery ; at necropsy both common carotid arteries were found to be thrombosed. Although only 24 years of age, his carotid vessels were markedly atheromatous, and clotting had evidently originated in each artery at the site of arterial puncture. This case is very exceptional, and apart from it no case treated by stage-ligation of the common carotid artery developed a post-ligation hemiplegia, whereas four out of eight cases treated by primary internal carotid ligation did. Primary common carotid ligation thus seems safer than primary internal carotid ligation, a conclusion which has already been stressed by Rogers (1949).

It is of course unnecessary to ligate the common carotid artery always in two stages, and often a complete ligation in a single stage will suffice. This is especially the case when arteriography of the opposite carotid artery, performed while the

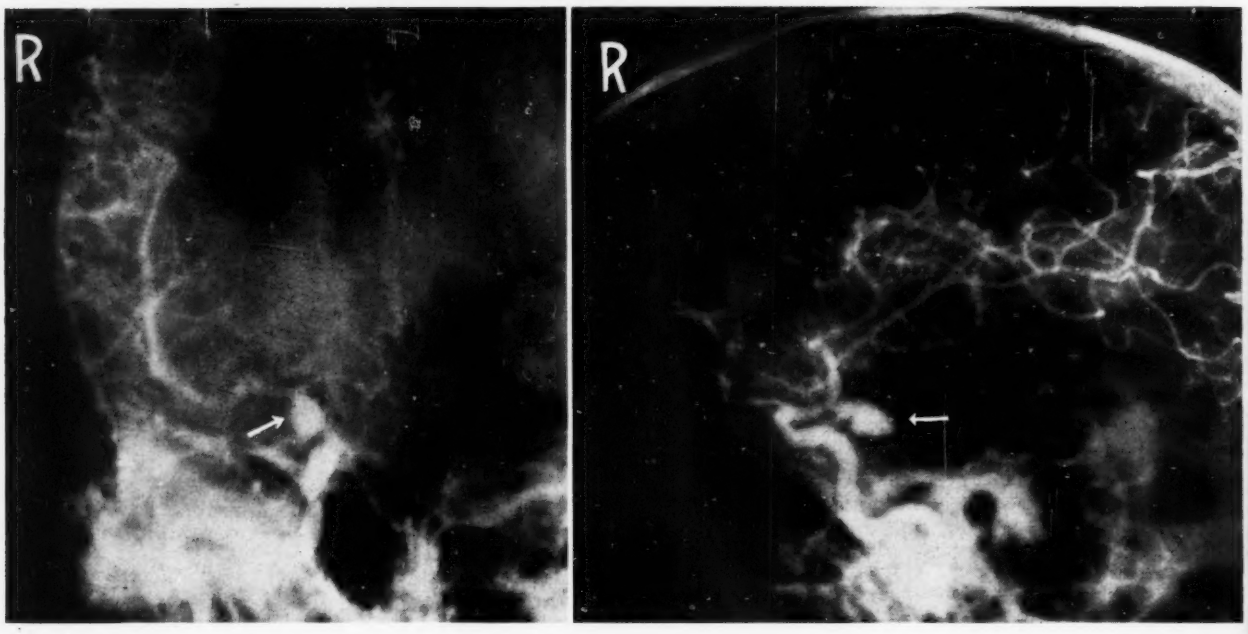


FIG. 5.—Anteroposterior and lateral arteriograms showing moderate-sized aneurysm (arrow) of intracranial internal carotid artery.

ipsilateral carotid is compressed, has disclosed an adequate collateral circulation through the circle of Willis. Failing such evidence, and especially in elderly people, it is wiser to play for safety and proceed slowly with ligation in two stages.

Need for Secondary Internal Carotid Ligation.—Common carotid ligation alone is not sufficient for many aneurysms of the intracranial portion of the internal carotid artery, but should always be followed by ligation of the internal carotid artery. Several of our observations indicate this. One patient, two weeks after stage-ligation of the common carotid artery had been concluded, developed a complete third-nerve palsy and had a fresh attack of subarachnoid bleeding. The internal carotid artery was then explored intracranially and a silver clip was placed across the artery just above the aneurysm. Immediately the sac of the aneurysm burst, and a brisk stream of blood welled up. This was controlled only when the lowest part of the intracranial internal carotid artery was clamped with an artery forceps. While the forceps was still in position, the internal carotid artery was exposed in the neck and ligated, after which the artery forceps was safely removed. Although the common carotid artery had been occluded previously, definite arterial pulsations were noted in the internal and external carotid arteries in the neck, although they were of lesser amplitude than normal. In a second patient, in whom the internal carotid artery was clipped intracranially above the aneurysm a few days after the common carotid artery had been tied in the neck, we had a similar experience of an aneurysmal sac bursting. These two cases demonstrate the power that can develop in the collateral circulation down the external carotid artery into the internal carotid artery, and indicate why common carotid ligation should be followed by internal carotid ligation*.

Need for Supplementary Intracranial Attack.—Probably in most cases ligation of the internal carotid artery (performed preferably following a preliminary common carotid ligation) is sufficient to give permanent relief. However, an aneurysm of this particular subgroup may continue to fill by reflux from the circle of Willis and may again cause trouble. Various observations suggest this.

Fairly often when performing arteriography of the contralateral carotid artery after the ipsilateral artery has been occluded, we have observed the contrast medium fill not only the anterior and middle cerebral arteries on both sides, but also the terminal portion of the intracranial internal carotid artery on the opposite side. This indicates that blood may reflux into the internal carotid artery from the

* Recently I have encountered a case in which aphasia together with weakness of the face and arm supervened 16 hours after a secondary internal carotid ligation. The ligature was released within two hours, and the artery did not seem thrombosed. Presumably arterial spasm had occurred. Recovery is proceeding gradually. Secondary internal carotid ligation is therefore not without its dangers.

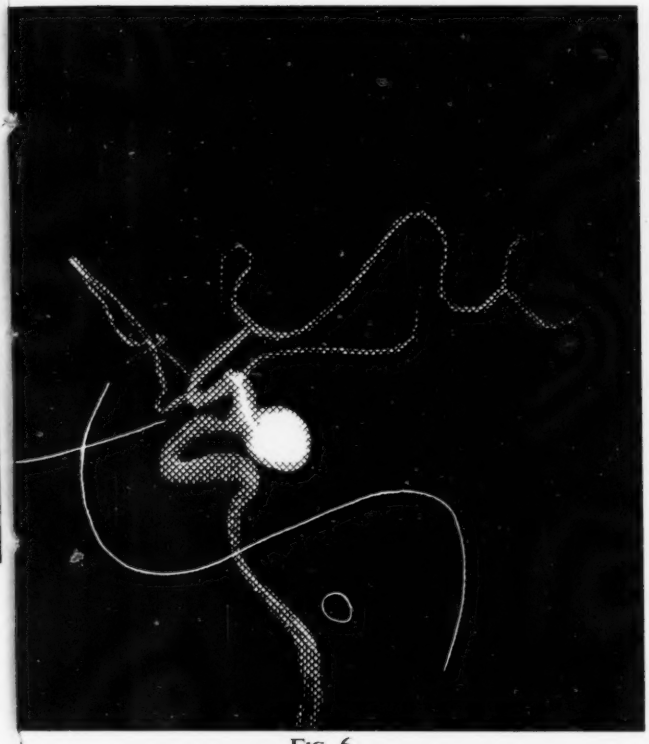


FIG. 6

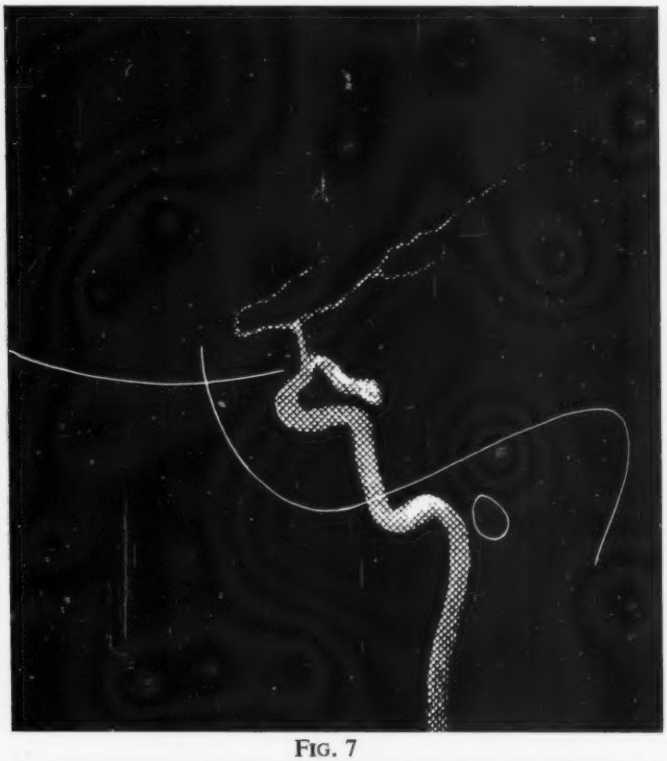


FIG. 7

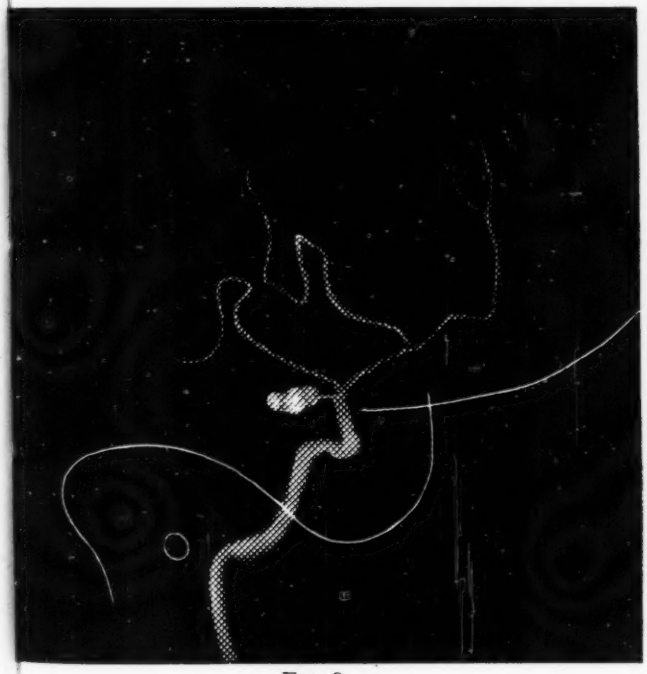


FIG. 8

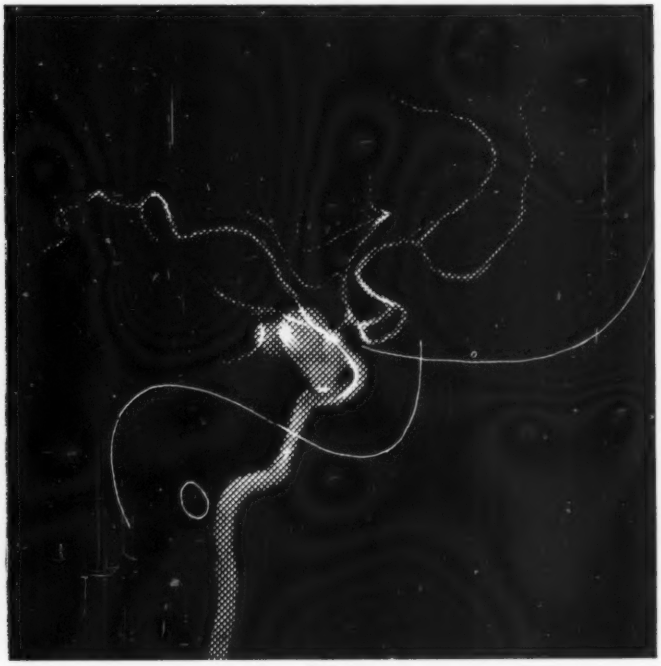


FIG. 9

FIGS. 6, 7, 8, and 9.—Tracings of arteriograms of other aneurysms of the intracranial internal carotid artery.

FIG. 10.—Photographs showing recovery of third nerve palsy. On the left, 14 days after carotid ligation and just before trapping, the left third nerve palsy (already improving slightly as eyelid is beginning to elevate) is seen. On the right, two and a half months later almost complete recovery is seen. (The left pupil is still slightly larger than the right; later it became of equal size.)

circle of Willis right from the time of carotid ligation. Again, in two cases of aneurysm in this particular subgroup, percutaneous arteriography of the opposite carotid artery was performed 15 or 16 months respectively after the ipsilateral internal carotid artery had been ligated. One of these cases had been complicated by a post-ligation hemiplegia, and in this case the aneurysm did not outline although both anterior and both middle cerebral arteries were filled; presumably there had been a spreading thrombosis of the internal carotid artery at the time of the hemiplegia and this had occluded the segment of the artery which bore the aneurysm. In the other case, which had not been complicated by a post-ligation hemiplegia, the new arteriograms outlined not only the anterior and middle cerebral arteries on both sides of the brain, but also a small pouch at the site of the aneurysm; evidently there had been no comparable spreading thrombosis and the aneurysm was still filling by reflux from the circle of Willis, although part of its lumen had thrombosed. That these surmises are probably correct was suggested by a third case, one originally presenting with a third-nerve palsy but without subarachnoid haemorrhage, and then treated by internal carotid ligation. Four years later this particular patient died of a ruptured aneurysm of the basilar artery, and at necropsy the original aneurysm on the internal carotid artery, although partly thrombosed, still had a lumen which filled by reflux from the circle of Willis.

Another observation emphasizing the advantages of intracranial surgery in aneurysms of this subgroup is that the ophthalmoplegia recovered completely in two out of three cases with a complete (as opposed to a partial) third cranial nerve palsy which were treated by trapping (Fig. 10), whereas only a partial recovery was observed in each of five cases with a complete third-nerve palsy treated only by carotid ligation. If the aneurysm is excluded from the circulation it presumably will thrombose completely, whereas it may not do this if it can still fill by reflux from the circle of Willis. Consequently, after completing carotid ligation, an intracranial attack was made in 10 patients, most of them being the more recent cases. All 10 patients survived, and nine made good recoveries. In each instance the aneurysm, being on the posterior aspect of the internal carotid artery, lay deep to the artery. In nine of the 10 cases the aneurysm was trapped by placing a silver clip across the internal carotid artery above the neck of the aneurysm and yet at the same time below the circle of Willis so that blood could still flow into the middle cerebral artery from the anterior cerebral artery. In the remaining case a homonymous upper-quadrantic hemianopia had been observed pre-operatively, and at operation a large haemorrhage was found within the temporal lobe adjacent to the aneurysm, and was sucked out from the mesial aspect of the temporal lobe. The aneurysm itself proved too high for clipping without simul-

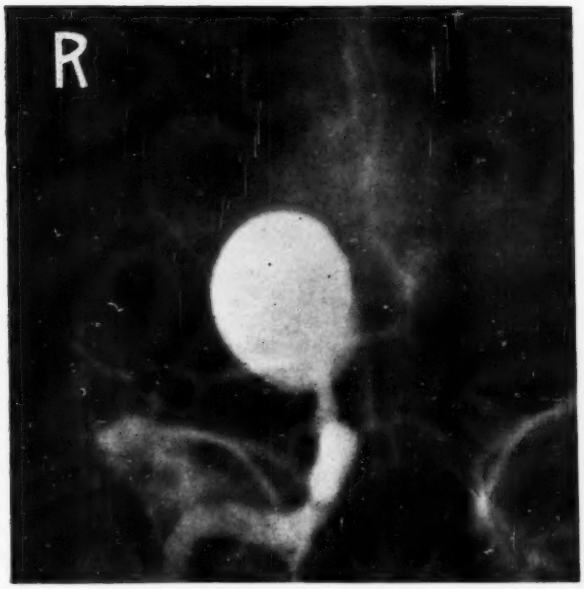


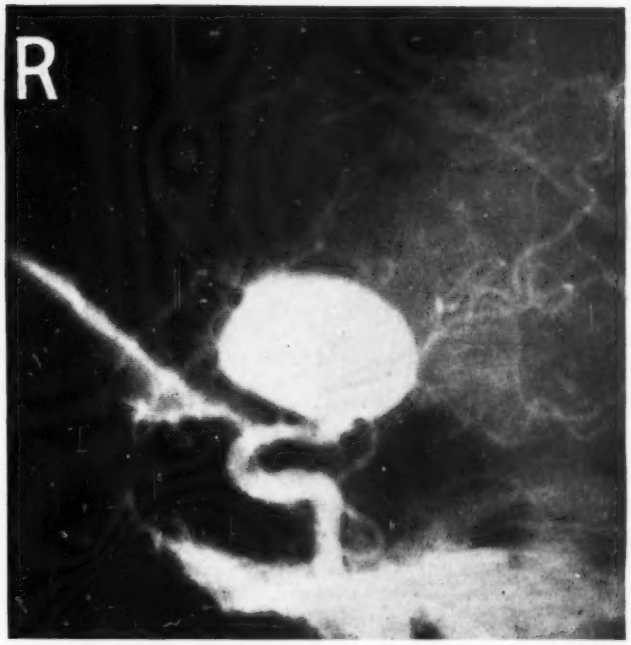
FIG. 11.—Arteriogram demonstrating large aneurysm at bifurcation of internal carotid artery.

taneously occluding the origins of the anterior and middle cerebral arteries, and so it was instead packed around with muscle pledgets. The patient made a good recovery, although, of course, he still has his hemianopic defect.

In the case in which the results of trapping were disappointing the patient towards the end of the first postoperative day developed a profound hemiplegia and aphasia which has persisted ever since (one year). Presumably a thrombosis of the internal carotid artery had spread upwards into the bifurcation from the region which was clipped; how frequently such a complication could be expected in a larger series of cases I do not know. Recently Matson and Woodhall (1948) reported another possible complication, viz. blindness of the homolateral eye, which presumably is due to infarction of the retina caused by a cessation of the blood-flow to the ophthalmic artery and its central retinal branch. Fortunately the collateral circulation of the retina is almost always adequate, and this complication of blindness was not seen in my series*.

Aneurysms at the Bifurcation of the Internal Carotid Artery

Four of our 50 patients had aneurysms in this situation, one patient having two aneurysms, one on each side of the circle of Willis. All five aneurysms



were treated by an intracranial attack which in two instances was preceded by common carotid ligation. All the patients survived, three making excellent recoveries, and one being left with a slight disability.

These results are particularly gratifying because Dandy (1944) at first regarded a direct attack on aneurysms in this situation as impracticable for fear that the origins of anterior and middle cerebral branches would be occluded. Later he had a case in which, after having first occluded the internal carotid artery with a clip, he caught one of these aneurysms in the mouth of a metal sucker and shrivelled it with the diathermy current. This method, however, is dangerous, for several of the aneurysms in various sites, which Dandy treated in this way, ruptured shortly afterwards.

Except for variations in size the arteriographic appearances were similar in each case, the aneurysm being seen in both the lateral and antero-posterior views as projecting upwards from the bifurcation (Figs. 11–13). In one case there was a slight hemiparesis and in another a subhyaloid haemor-

* In another recent case a hemiplegia developed about 20 hours after intracranial trapping. Drowsiness, and then coma, supervened, and the patient died on the fourth day. Post-mortem examination showed necrotic changes in the territory of the middle cerebral artery, but the artery itself was not thrombosed, neither was the anterior cerebral artery nor the internal carotid artery at its bifurcation. Presumably arterial spasm had occurred in this case also.

FIG. 12

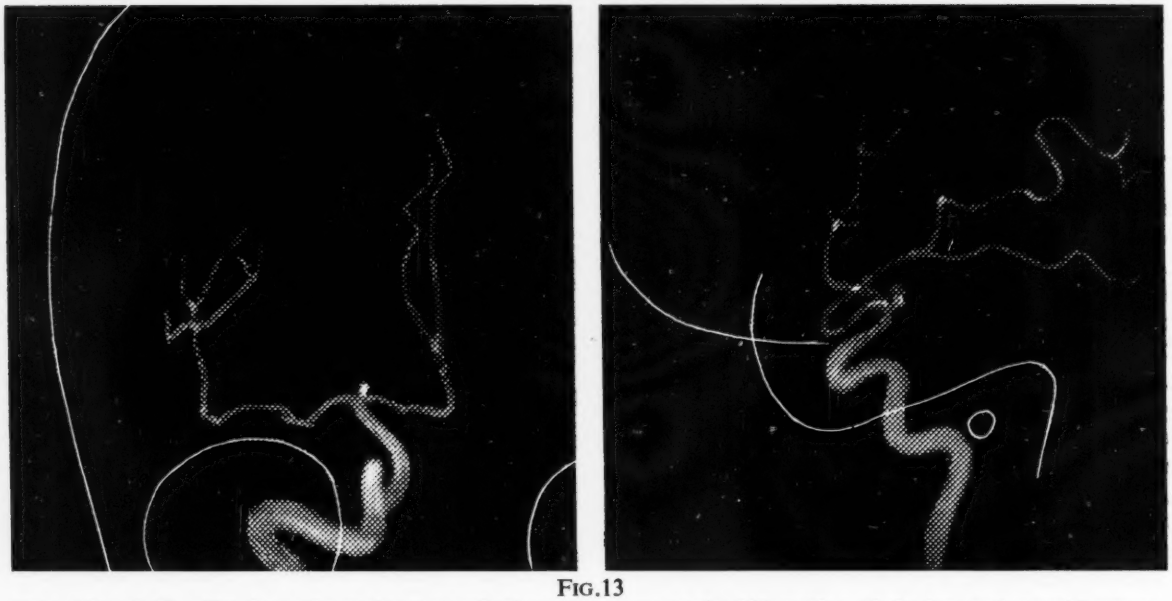


FIG. 13

FIGS. 12 and 13.—Tracings of arteriograms of other aneurysms at the bifurcation of the internal carotid artery.

rhage, but as a group these aneurysms are generally without localizing signs.

Carotid ligation cannot have more than a temporary effect with aneurysms in this situation, for once the collateral circulation builds up, the blood pressure within these aneurysms must reach former levels. It was utilized in one of my cases, but in this case as well as in the other three cases, the chief resort was to a direct intracranial attack. A variety of methods for dealing with the aneurysm was employed. In the first two cases, both with aneurysms less than 5 mm. in diameter and so too small to " take " a clip, the lesion was treated by wrapping with muscle. In the third case, one with an enormous aneurysm complicated by hemiparesis, the medial and lateral sides as well as the anterior aspect of the aneurysm were wrapped with a layer of surgical gauze as well as muscle, after preliminary carotid ligation had been carried out. This patient has since continued to show a persisting hemiparesis, of moderate severity, but she is able to do all her housework. In the fourth patient, who had two aneurysms, the neck of each aneurysm was sufficiently narrow to be occluded by a clip. The case

history of this particular patient has been reported elsewhere (Falconer, 1950).

From my experience of this subgroup I feel that aneurysms situated at the bifurcation of the internal carotid artery may be treated in the first instance by carotid ligation, but that wherever possible this should be followed by an intracranial approach.

Aneurysms of the Middle Cerebral Artery

There were 10 cases in my series, seven of which made good recoveries, one recovered with an appreciable disability, and two died. Three cases exhibited massive haemorrhages within the temporal lobe, and only one of these recovered. One of the fatal cases had two aneurysms, one on each middle cerebral artery. My impression is that aneurysms in this subgroup should be treated whenever possible by an intracranial attack with wrapping of muscle around the aneurysm, as probably the best local measure. Any associated intracerebral clot should be removed.

Few reports of operations on aneurysms of the middle cerebral artery appear in the literature. Dandy (1944) reported having operated on four cases, but without any successful result. Since then Swain (1948) records having operated on three cases with success in two. Swain approached each aneurysm either across the Sylvian fissure or by an incision through the temporal lobe. He then caught the fundus of the aneurysm in the mouth of a metal sucker, and simultaneously coagulated it with a diathermy current. This method, however, when used by Dandy for aneurysms in other situations, often proved hazardous, as in several cases delayed rupture of the aneurysm occurred. Recently Sweet, Sarnoff, and Bakay (1950) have recorded a case in which internal carotid ligation was performed for an aneurysm of the middle cerebral artery. Eighteen months later their patient had another attack of subarachnoid haemorrhage, this time with hemiparesis of the opposite side. They therefore presumed that the aneurysm of the middle cerebral artery was again causing symptoms, and that it was being supplied from the carotid artery of the opposite side as well as from the basilar system. Consequently they exposed the opposite common carotid artery under local analgesia, and clamped it for a period of 30 minutes. As anoxic symptoms had not appeared during the period of clamping, they then ligated the exposed common carotid artery. Thus this case of middle cerebral aneurysm in effect was treated by bilateral carotid ligation, a testimony to the way in which the basilar artery will sometimes take over the functions of both cerebral arteries. No attempt apparently was made at a direct intracranial exposure.

The arteriographic appearances in this subgroup of aneurysms are likewise characteristic, and require a good antero-posterior view as well as a lateral view for their proper interpretation (Figs. 14–17). In the lateral views the aneurysm shows up clearly, but may appear superimposed upon the bifurcation of the internal carotid artery. With this projection alone it may be impossible to distinguish these from aneurysms arising at the bifurcation or sometimes even on the anterior communicating artery. In antero-posterior views, however, the aneurysm is depicted on the middle cerebral artery, usually at its first point of branching about 2 cm. distal to the bifurcation. But, as in this projection the aneurysm is at a much greater distance from the film than in the lateral view, its edges are usually indistinct and its size seems greater than in the lateral view.

Experiences with Carotid Ligation.—Seven of my cases were treated in the first instance by carotid ligation on the same side of the neck (primary stage-ligation of the common carotid artery, six cases ; primary internal carotid ligation, one case). In four cases this was the only surgical treatment, largely because in three of these four cases the carotid ligation was followed by hemiplegia. In one of these three cases, a woman of 66 years, the hemiplegia appeared suddenly six days after stage-ligation of the common carotid artery had been completed, and fortunately within a few days it began to improve so that after a short period there was little trace of it. In the second case, a woman of 55 years, the common carotid artery was tied in two places and divided between them, a method of ligation recommended by Rogers (1947) as minimizing the risk of hemiplegia ; yet a hemiplegia appeared within 24 hours and persisted for five months before finally disappearing. In the third patient, a man of 28 years, the left common carotid artery was successfully ligated in two stages followed by left internal carotid ligation in a further stage. Three days after the ligation had been completed the patient awoke from sleep unable to raise his right arm and unable to speak properly. Heparin therapy was started forthwith for a period of 24 hours, but observations were made which in retrospect suggest that spasm of cerebral arteries was responsible for this complication rather than embolism or thrombosis. First, the laboratory reports when they came to hand showed that the blood coagulation time was within normal limits, but that the prothrombin concentration in the blood had been only 40% of normal when heparin therapy was begun. This seemed an argument against a clotting diathesis. Secondly, a procaine

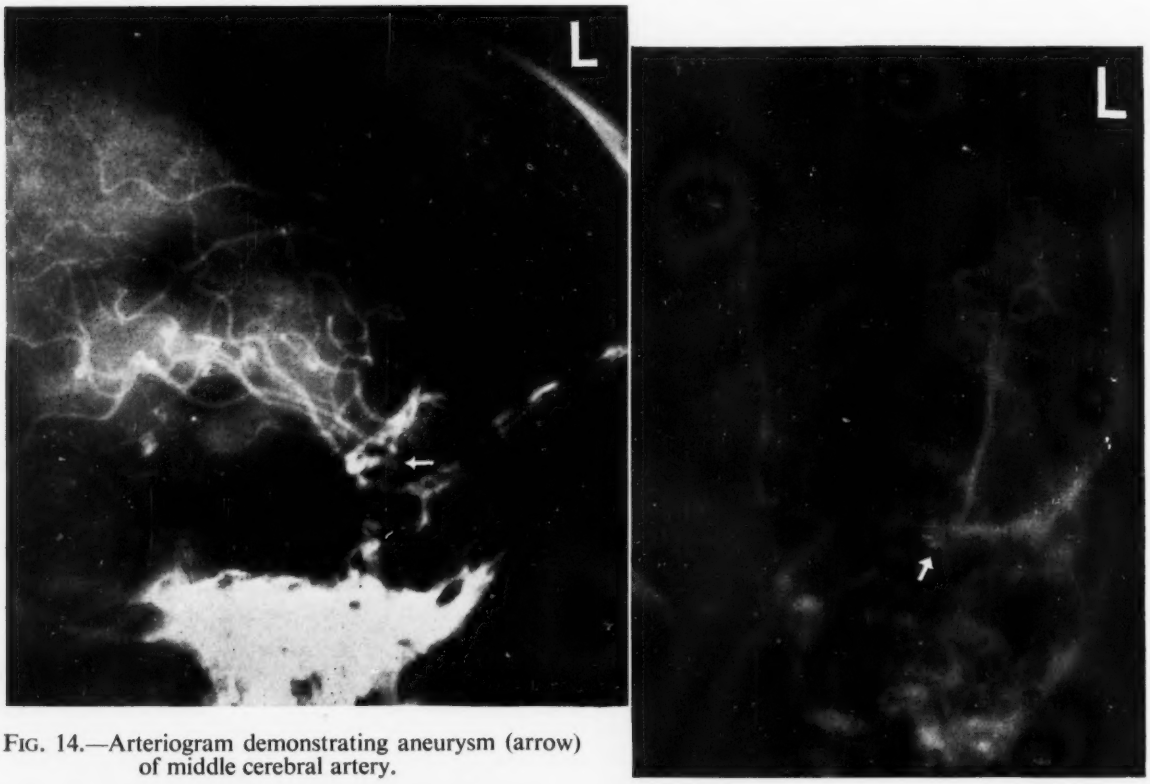


FIG. 14.—Arteriogram demonstrating aneurysm (arrow) of middle cerebral artery.

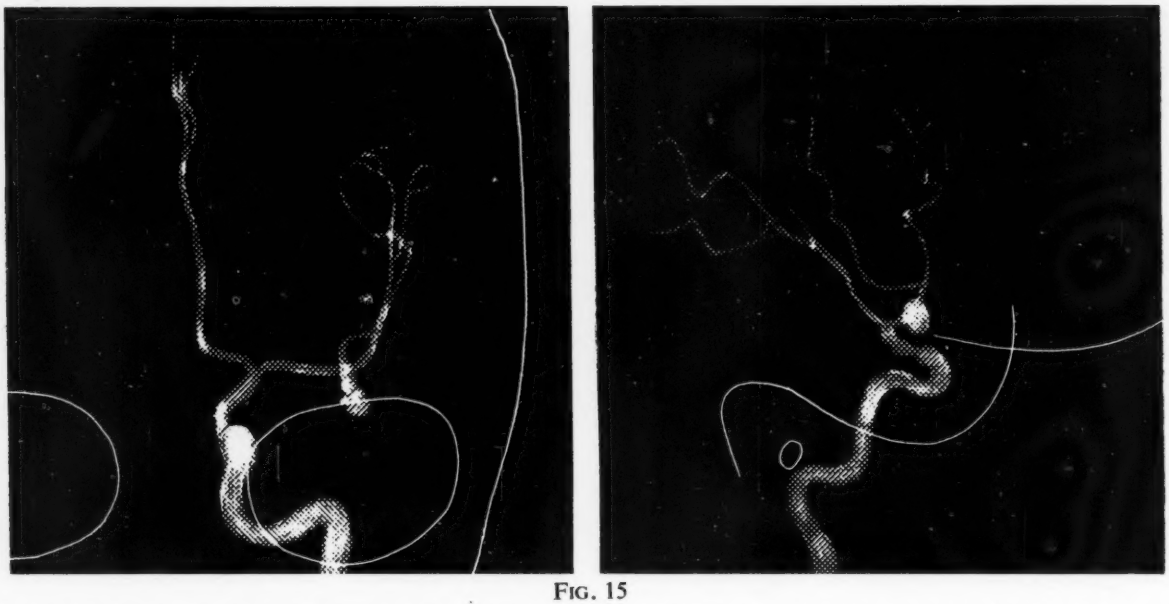


FIG. 15

block of the stellate ganglion produced prompt improvement which lasted for about three hours. This was followed by repeated injections of tetraethyl ammonium-bromide solution (2 ml. intramuscularly every two hours), each injection being associated with steady improvement. Thirdly, in this particular patient, when a percutaneous arteriogram was performed on the opposite carotid artery several weeks afterwards, the left middle cerebral artery and the aneurysm appeared to fill normally.

From these cases, and also from another case, in which a partial common carotid occlusion was attempted but was not tolerated because of anoxic symptoms, it would seem that common carotid

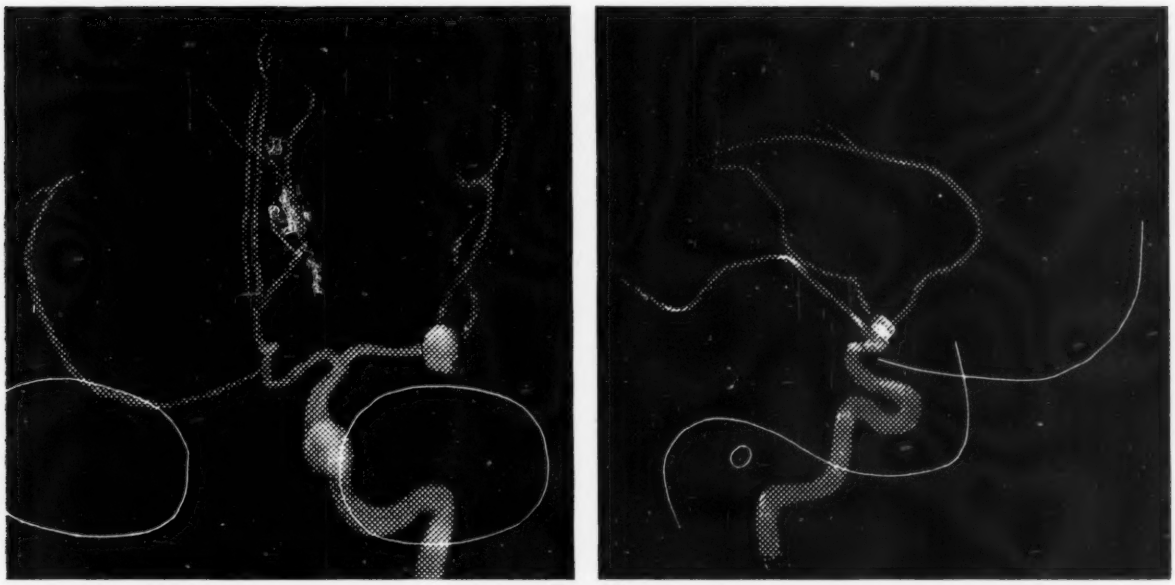


FIG. 16

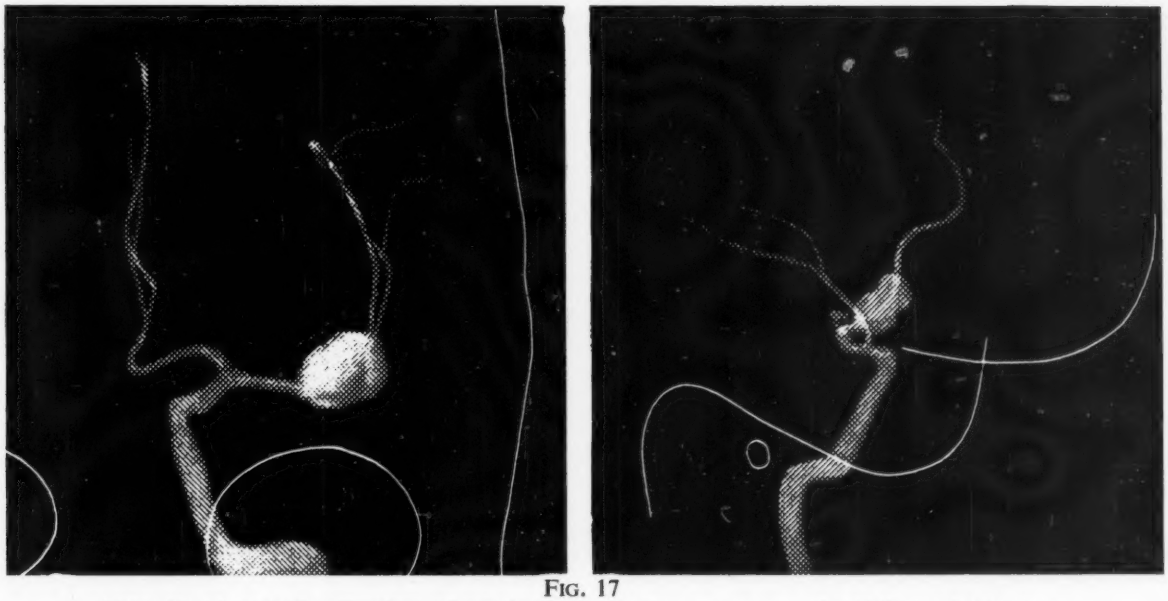


FIG. 17

FIGS. 15, 16, and 17.—Tracings of arteriograms of other aneurysms of middle cerebral artery.

ligation carries increased hazards in the presence of an aneurysm of the middle cerebral vessels, and that arterial spasm plays a part in producing symptoms.

Experiences with Intracranial Operation.—Six cases were submitted to an intracranial operation, which in three instances was preceded by common carotid ligation. In each instance the fissure of Sylvius was opened up as described earlier, and the aneurysm was well seen. Three of the patients made excellent recoveries; one recovered with a hemiplegia; and two died.

The three cases which made good recoveries were treated in two instances by wrapping the aneurysm with muscle, and in one by clipping the neck of the aneurysm. In one of these cases the aneurysm was associated with a large temporal lobe haemorrhage which was successfully sucked out. In the case that recovered with a hemiplegia, an attempt was made at operation to clip the neck of the aneurysm, but the clip tore the sac causing brisk bleeding which was then controlled by wrapping with muscle. The two cases which ended fatally were both found at operation to have large clots within the temporal lobe, and these clots were

evacuated. At the subsequent necropsy each temporal lobe was found to be extensively lacerated. In one of the two fatal cases a second and smaller aneurysm was found on the opposite middle cerebral artery, as had been previously suggested by the arteriograms.

An interesting but unexplained observation is that in eight of my 10 cases the leaking aneurysm was located on the left middle cerebral artery in the dominant hemisphere. Four of these cases exhibited aphasia after operation, but in three the aphasia was transient.

Aneurysms of the Anterior Cerebral Artery

This subgroup ranked second in numerical size to aneurysms of the intracranial internal carotid artery. There were 17 cases, and these were treated surgically with 10 good results, two recoveries with persisting disability, and five deaths. These aneurysms are a more difficult proposition to treat than are the aneurysms of the internal carotid artery. Often they are readily supplied with blood from both internal carotid arteries, and so carotid ligation may not be effective. Again, leaking aneurysms in this situation, like aneurysms of the middle cerebral artery, are likely to cause massive intracerebral haemorrhage (into the frontal lobes) as well as subarachnoid haemorrhage (Richardson and Hyland, 1941). For these reasons a direct intracranial attack is frequently necessary in order to save life.

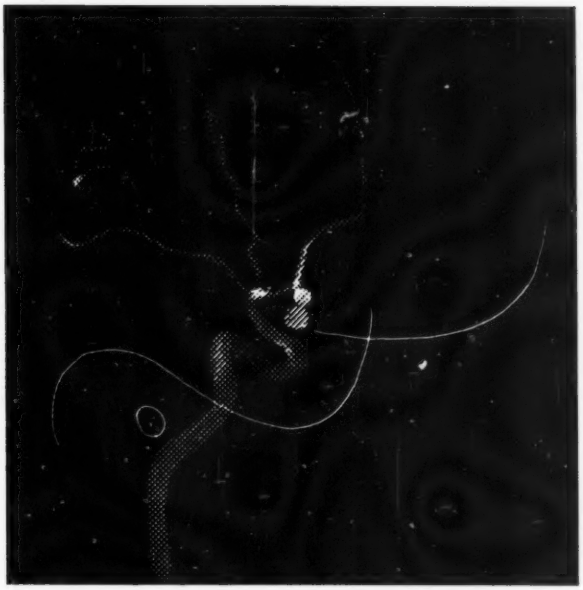
Dandy (1944) evidently encountered at operation six cases in this situation, and had success in two of these. Only two of his cases gave a history of recent bleeding, and both of these died. However, there are six reports in the literature where an aneurysm of the anterior cerebral artery, that had recently bled, was successfully attacked. Tönnis (1936) after having located by arteriography an aneurysm on the anterior communicating artery, attempted to expose it by a subfrontal approach, but was unsuccessful. He then retracted the mesial surface of the frontal lobe from off the falx, and split the anterior part of the corpus callosum. In this way he came down upon the aneurysm from above, and covered it with muscle. Cone (quoted by Russel, 1939), operating on a case, in which air-encephalography had disclosed a space-occupying lesion in the inferior frontal region, evacuated a clot from the frontal lobe, and found a small aneurysm on the anterior communicating artery projecting into the operation cavity. This he was able to excise. List and Hodges (1946), having demonstrated by arteriography an aneurysm on the left anterior cerebral artery close to the bifurcation, exposed the subfrontal portion of the anterior cerebral artery, and placed silver clips on this artery on either side of the aneurysm with an excellent result. Sugar and Tinsley (1948) described a case of aneurysm of the distal part of the anterior cerebral artery in which, some time after an attack of subarachnoid haemorrhage, they clipped the artery a little proximal to the aneurysm. Recently Elvidge and Feindel (1950) reported that they had successfully dealt with two cases of aneurysm in relation to the anterior communicating artery. In one they clipped the anterior cerebral artery on either side of the communicating artery, before clipping the aneurysm itself. In the other case they excised the sac. Besides these six cases with subarachnoid bleeding, McConnell (1937) and Dandy (1944) have each reported a case in which they encountered a large, thick-walled aneurysm causing chiasmal compression, and had incised the aneurysm, packing muscle into its interior. Dandy (1944) also described a case in which he successfully excised a large aneurysm in this region, presumably at the same time sacrificing a segment of one anterior cerebral artery.

As the surgical problems differ according to which part of the anterior cerebral artery is involved, my 17 cases will be considered in three sections, as follows :—

	Cases
(1) aneurysms of the proximal portion of the artery	2
(2) aneurysms involving the anterior communicating artery	11
(3) aneurysms of the distal portion of the artery	4

(1) Aneurysms of the Proximal Portion of the Artery.—There were two cases, both of which were treated by an intracranial attack. Both survived, but the result in the first case was disappointing because of an unexpected complication. In both cases the aneurysm was situated on the anterior cerebral artery a little proximal to the communicating artery, and the arteriographic appearances are illustrated in Figs. 18 and 19. Possibly these two cases may have been examples of the more common subgroup of aneurysms in relation to the communicating artery, although at operation they appeared away from that artery.

In the first case (Fig. 18) a small aneurysm was exposed on the left anterior cerebral artery immediately above the left optic nerve, and was treated by clipping the anterior cerebral artery close to the bifurcation. I had anticipated that this procedure would carry very little risk, because List and Hodges (1946) had successfully trapped an aneurysm in this same situation, and because the arteriograms had shown that, distal to the communicating artery, both anterior cerebral arteries were receiving their



FIGS. 18 and 19.—Tracings of arteriograms of aneurysms of the proximal portion of the anterior cerebral artery.

major supply from the internal carotid of the opposite side. However, on the second postoperative day the patient unexpectedly developed pronounced aphasia and a right-sided hemiparesis which affected principally his arm, and not his leg, as might probably be expected with a thrombosis of an anterior cerebral artery. Postoperative arteriograms, however, confirmed that the clip had been placed on the left anterior cerebral artery, and that only the segment of the artery proximal to the communicating artery was thrombosed. The patient has now been followed for three years, and still exhibits a residual aphasia and hemiparesis.

The explanation presumably lies in the existence of Heubner's artery (medial striate artery) described in such a masterly fashion by Critchley (1930). One of the basal perforating branches of the circle of Willis, this artery normally arises from the anterior cerebral artery, but sometimes instead from the middle cerebral artery or even from the internal

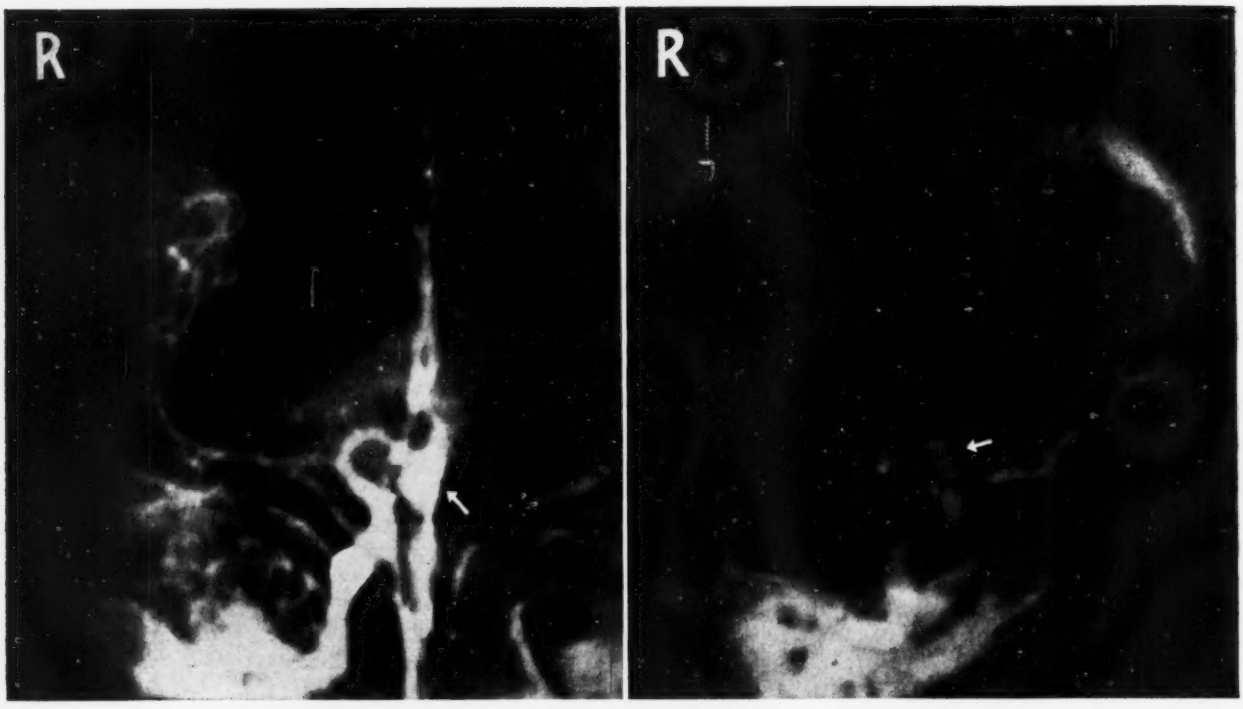


FIG. 20.—Arteriogram demonstrating aneurysm (arrow) projecting downwards and forwards from the anterior communicating artery.

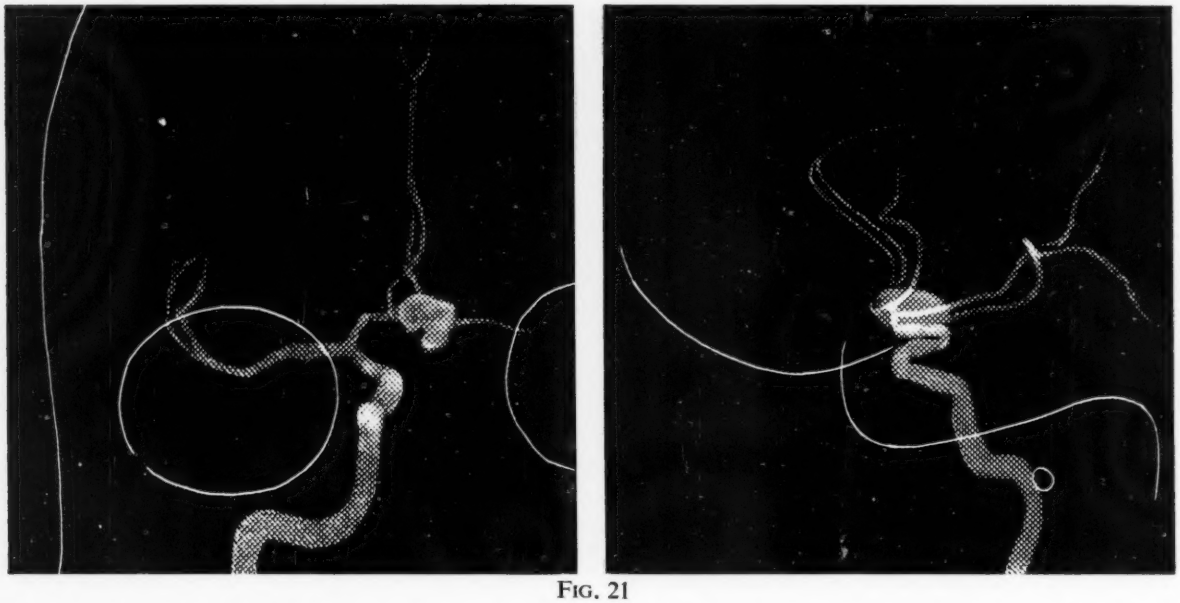


FIG. 21

carotid artery. It enters the anterior perforated substance, and is distributed to the anterior part of the caudate nucleus and anterior third of the putamen, to the tip of the globus pallidus, and to the anterior limb of the internal capsule. Its occlusion is characterized by hemiplegia with motor paralysis predominating in the arm rather than in the leg, and associated with a slight sensory disturbance and with aphasia should the dominant hemisphere be involved. Although we never saw Heubner's artery at operation, it may have arisen from the anterior cerebral artery distal to the point of clipping and affected by the thrombosis of this vessel.

After this experience the next aneurysm encountered in this same situation (Fig. 19), was, after exposure, merely wrapped round with pledgets of hammered muscle. The patient made a gratifying recovery. My experience with these proximal anterior cerebral aneurysms, however, is still too

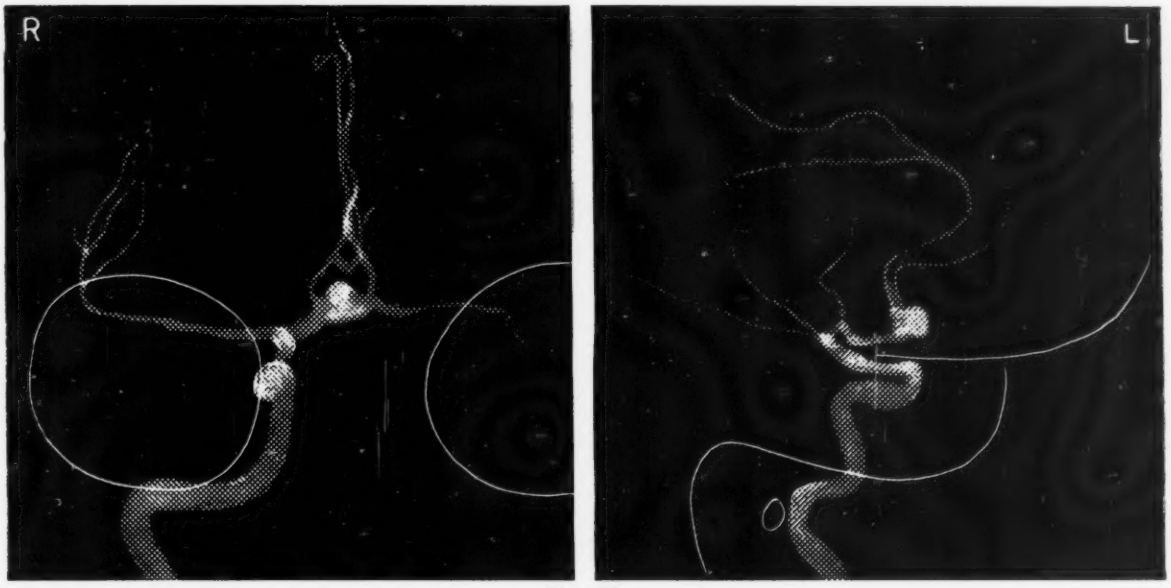


FIG. 22

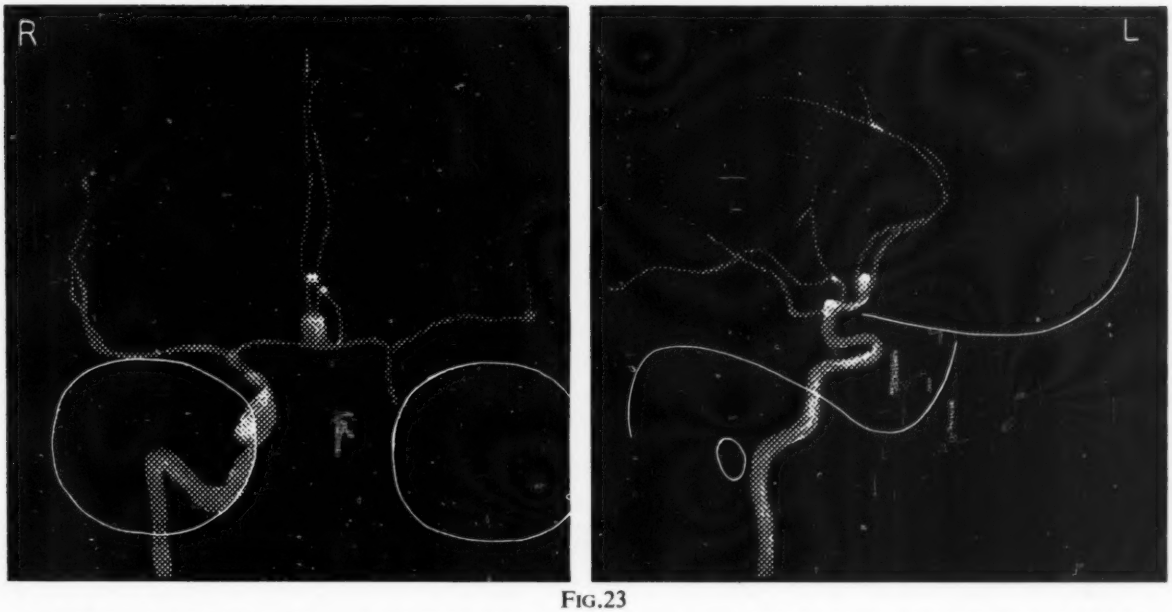


FIG.23

FIGS. 21, 22, and 23.—Tracings of arteriograms of other aneurysms of the anterior communicating artery.

scanty to permit of generalizations about the best method of treatment.

(2) Aneurysms Involving the Anterior Communicating Artery.—There were 11 cases, seven of which made good recoveries, one recovered with a peculiar mental disability, and three died. Three cases were associated with intracerebral haemorrhage, in two instances into the frontal lobe, and in one into the corpus callosum. The conclusion reached was that, whenever practicable, these aneurysms are best treated by an intracranial approach, exposing the aneurysm and wrapping it around with hammered muscle.

The arteriographic appearances of these aneurysms have a common pattern (Figs. 20 to 23). In antero-posterior views the aneurysms are situated in the midline, or almost so, between the two anterior cerebral arteries, while in lateral views the aneurysmal sac projects either downwards and forwards, or upwards and backwards. In five out of our 11 cases there was an anomaly of the circle of

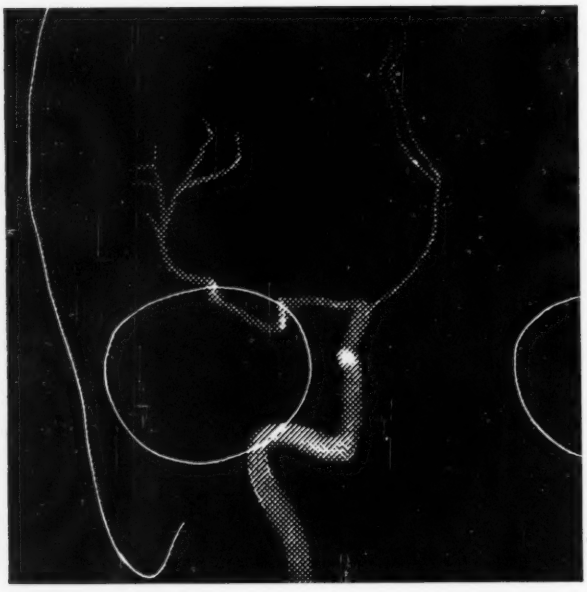


FIG. 24.—Tracing of arteriogram showing shift of the right anterior cerebral artery to the left side, indicating a space-occupying lesion within the frontal lobe.

Willis, such that, distal to the communicating artery, both anterior cerebral arteries were supplied from one carotid artery only, suggesting a deficiency in the circle of Willis between the anterior communicating artery and the internal carotid artery of the opposite side. In the remaining cases the aneurysm was shown up by arteriography of carotid artery on either side (see Figs. 22 and 23).

Experiences with Carotid Ligation.—Three cases were treated by carotid ligation alone, and two died. The first of these, an obese woman, who was deeply unconscious when referred, died two days after a primary ligation of the left internal carotid artery. Necropsy revealed the vascular anomaly mentioned above (which the arteriograms had clearly indicated, but we had not recognized), only a thread-like vessel completing the circle of Willis between the anterior communicating artery and the opposite internal carotid artery. The occluding of the left internal carotid artery had virtually shut off the blood flow to both anterior cerebral arteries and so produced infarcts in both frontal lobes. In the second case, the presence of this vascular anomaly was recognized from the arteriograms, and treatment was therefore limited to a stage-ligation of the common carotid artery, apparently with success. In the third case the arteriograms were of poor quality and did not show any aneurysm, but they did disclose an

FIG. 25.—Base of brain viewed from in front. A small aneurysm (arrow) can be seen on the left anterior cerebral artery where it is supported by a white rod. Notice a large clot occupying the mesial surface of the right frontal lobe.

appreciable shift of both anterior cerebral arteries to the left side, indicating a large haemorrhage within the right frontal lobe (Fig. 24). We therefore presumed that there was a bleeding aneurysm in the right anterior cerebral artery, and so went ahead and tied the right common carotid artery in the neck. Six hours later the patient suddenly became unconscious and died within a few minutes. At necropsy a small aneurysm was found on the opposite or left anterior cerebral artery, in the angle between that artery and the anterior communicating artery, and this aneurysm had ruptured across the midline to produce a large haemorrhage within the right frontal lobe (Fig. 25). I have since seen in museum specimens other examples of an aneurysm situated on one anterior cerebral artery rupturing into the frontal lobe of the opposite side. Such cases show that, in deciding the side of a bleeding lesion, reliance cannot always be placed upon the direction of the shift of the arterial tree as shown by an arteriogram of one side only, but that both carotid arteries may have to be injected before an aneurysmal sac is revealed.

These three cases taken by themselves cannot be regarded as a fair test of either common or internal carotid ligation for this subgroup of aneurysms, but they do indicate that these procedures cannot be applied in all such cases without proper safeguards. Occlusion of either carotid artery, moreover, can only have a temporary effect in lowering the intra-arterial pressure within the communicating artery pending the development of the collateral circulation. This is especially true when the preoperative arteriograms show that the aneurysm can be filled from either carotid artery. Therefore, we have come to regard a direct attack on these aneurysms, with or without preliminary carotid ligation, as the measure most likely to give permanent relief.

Experiences with an Intracranial Attack.—A direct attack was undertaken in the remaining eight cases in this section with six good recoveries, one recovery with mental impairment, and one death from recurrent bleeding. In four instances the intracranial attack was preceded by stage-ligation of the common carotid artery, but this measure was not considered worthwhile when the aneurysm could be shown up by carotid arteriograms. The six successful cases were each treated by wrapping hammered muscle around the aneurysm. One of the aneurysms was associated with a haemorrhage, the size of a walnut, in the genu of the corpus callosum, and this haemorrhage was also evacuated. We learnt that most aneurysms in this region appear to project forwards and downwards from the anterior communicating artery, but that a few project upwards and backwards. The distinction can be readily determined from the arteriograms, and is of practical importance because, whereas the first type can often be readily exposed by a subfrontal approach alone, the second type requires the combined subfrontal and vertical approaches.

The case that died was the only one in my experience so far to suffer recurrent bleeding after a surgical attack. Two craniotomies proved necessary. At the first the aneurysm was exposed by a combined vertical and subfrontal approach, and unfortunately burst in the later stages of the manipulations to uncover it. The bleeding, however, was controlled by wrapping with hammered muscle, and the patient at first appeared to be progressing well. Three weeks later she was sent home and a few days after that she had a sudden recurrence of subarachnoid haemorrhage, necessitating her readmission. The craniotomy was reopened and a small haemorrhage within the right frontal lobe was sucked out, but the region of the anterior communicating artery was so covered with organizing muscle tissue that I was unable to define the vessels or see the bleeding point. As an alternative I then clipped the right anterior cerebral artery proximal to the communicating artery, hoping that this would lessen the blood flow through the aneurysm. For the next seven weeks the patient lay in a mute, disinterested, and motionless state before succumbing from bronchopneumonia. At necropsy the aneurysm was found still embedded in muscle. There was extensive destruction of the right frontal lobe, and there was also an area of cortical destruction about 4 cm. $\times$ 2 cm. on the mesial aspect of the left frontal lobe. Evidently the muscle patch used to seal the aneurysm at its first operation must have given way at the time of recurrence. In several subsequent cases we tried wrapping the aneurysm with a single layer of surgical gauze as a filigree, in addition to wrapping it with muscle.

The case of the patient, who following operation exhibited considerable mental impairment, was also instructive because it would appear that both anterior cerebral arteries were occluded. In this patient, a farm worker of 28 years, referred to us after his seventh bout of subarachnoid haemorrhage, bilateral percutaneous carotid arteriography disclosed a moderate-sized aneurysm, which we interpreted as projecting downwards and forwards from the right anterior cerebral artery, just proximal to the communicating artery (Fig. 26). Distal to the communicating artery both anterior cerebral arteries could be readily filled from either carotid artery indicating a free collateral circulation through the communicating artery. A right frontal craniotomy

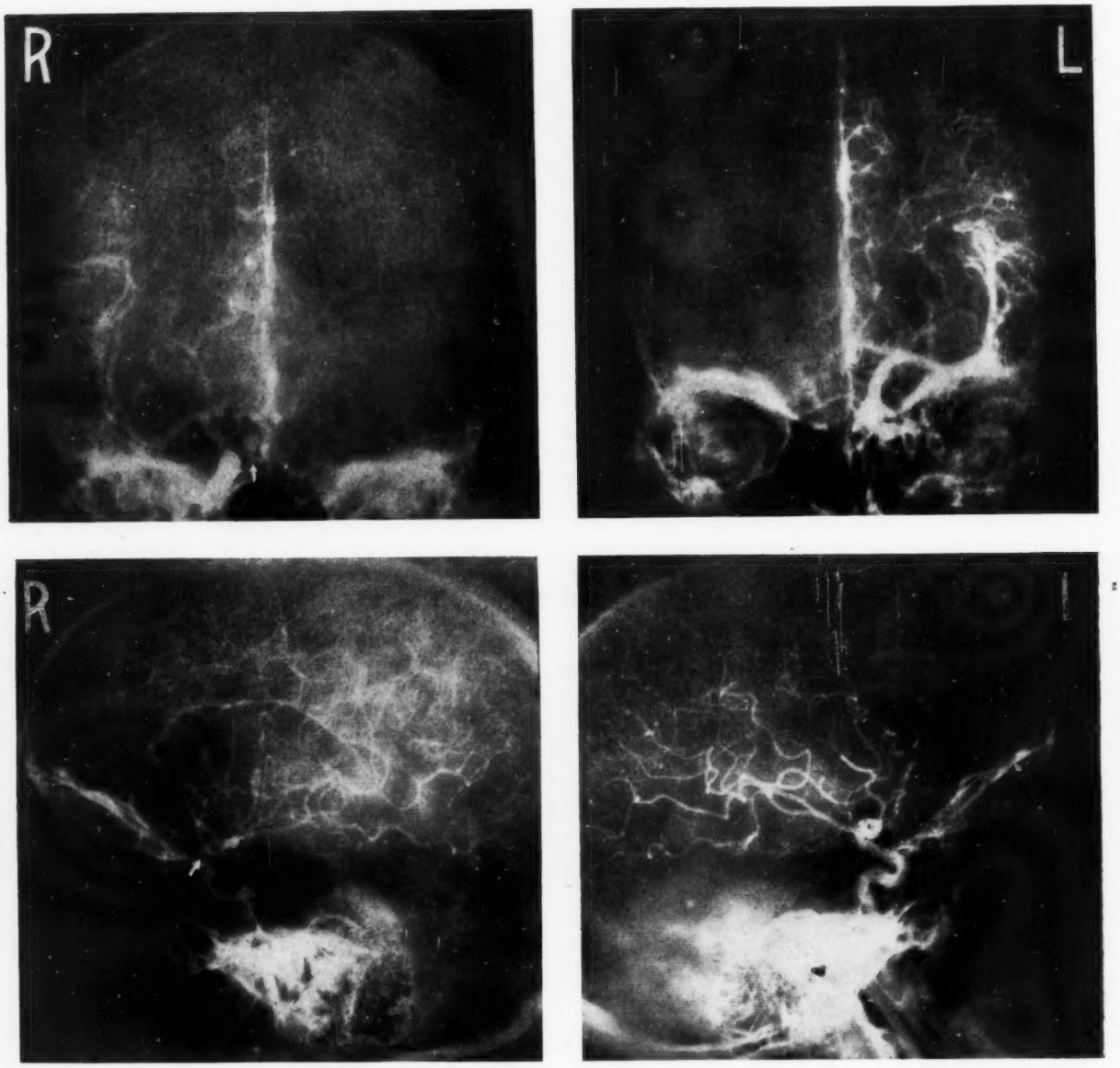


FIG. 26.—Right carotid arteriograms show aneurysm (arrow) which was interpreted as arising from the right anterior cerebral artery, but which probably arose from the anterior communicating artery. Left carotid arteriograms, shown for comparison, are normal.

was performed, and the first part of the anterior cerebral artery was exposed. An aneurysm was clearly displayed projecting downwards and forwards close to the midline. Its neck was then clipped, but unfortunately it tore and bled, and so the artery itself was hastily occluded with a second clip placed across it at the point where the aneurysm was attached, and the aneurysmal sac was coagulated with diathermy. At the time I thought that I had clipped the right anterior cerebral artery just proximal to the communicating artery, and I anticipated a good recovery, for the preoperative arteriograms had indicated that the distal part of the right anterior cerebral artery would be well supplied through the communicating artery. However, although the patient's physical convalescence was smooth, he has since operation exhibited profound disturbances of recent memory and of initiative. For several months after operation he used to walk around the ward in a cheerful and cooperative state, and without any motor disorder. He would readily enter into conversation, and he

could promptly and accurately recall events from his past life, as well as describe his home surroundings. But he was disorientated as regards the present and he could not remember things that had happened or been told to him a few minutes earlier. He read voraciously, but without remembering a few minutes later what he had read, and he wrote long newsy letters home, full of imaginary events and doings. After some months some improvement was noted, but, although he had then returned to work on his parent's farm, he has still to be directed and supervised, and his recent memory is still very poor.

We were naturally concerned with this unexpectedly poor result, and so several weeks after operation we repeated the percutaneous arteriogram (Fig. 27). The new views showed, first that the occluding clips were in the midline in the position of the anterior communicating artery ; and secondly that the trunks of the anterior cerebral arteries in this vicinity were occluded. Instead, distal to this site of occlusion the blood-flow through each anterior cerebral artery was being maintained by an anastomotic circulation coursing over the superior margin of the frontal lobe from the corresponding middle cerebral artery. In retrospect it seems likely that the aneurysm was situated on the anterior communicating artery rather than on the right anterior cerebral artery, and that the anterior communicating artery was the vessel which was clipped with perhaps the two anterior cerebral arteries at either end of it. Elvidge and Feindel (1950) in reporting the case of aneurysm of the anterior communicating artery which they had excised, describe a postoperative mental state similar to that observed in my patient. It is possible that in their operative manipulations they too occluded both anterior cerebral arteries in the vicinity of the communicating artery.

(3) Aneurysms of the Distal Portion of the Artery.—There were four examples, and they were treated surgically with two deaths and two good recoveries. Although our experience is still scanty, our observations suggest that these aneurysms are often associated with a massive intracerebral haemorrhage (all four cases had haemorrhages within one or both frontal lobes), and that in treating these cases it is important that these haemorrhages should be evacuated. Consequently an intracranial attack is called for. As regards local measures, these aneurysms can often be safely treated either by clipping the anterior cerebral artery immediately proximal to the aneurysm or by trapping the aneurysm between clips applied to the artery on either side of it.

In arteriograms these aneurysms show up as shadows on the anterior cerebral artery, usually at a point of branching in its pericallosal course (Figs. 28, 30, and 31). If there is a massive intracerebral haemorrhage confined to one frontal lobe, the aneurysm with the adjacent portion of the anterior cerebral artery will usually be displaced to the opposite side, but if bilateral frontal lobe haemorrhages are present (as in one of our cases) the aneurysm may still be in the midline. If there is a free collateral circulation through the anterior communicating artery the aneurysm may be outlined by injection of either carotid artery.

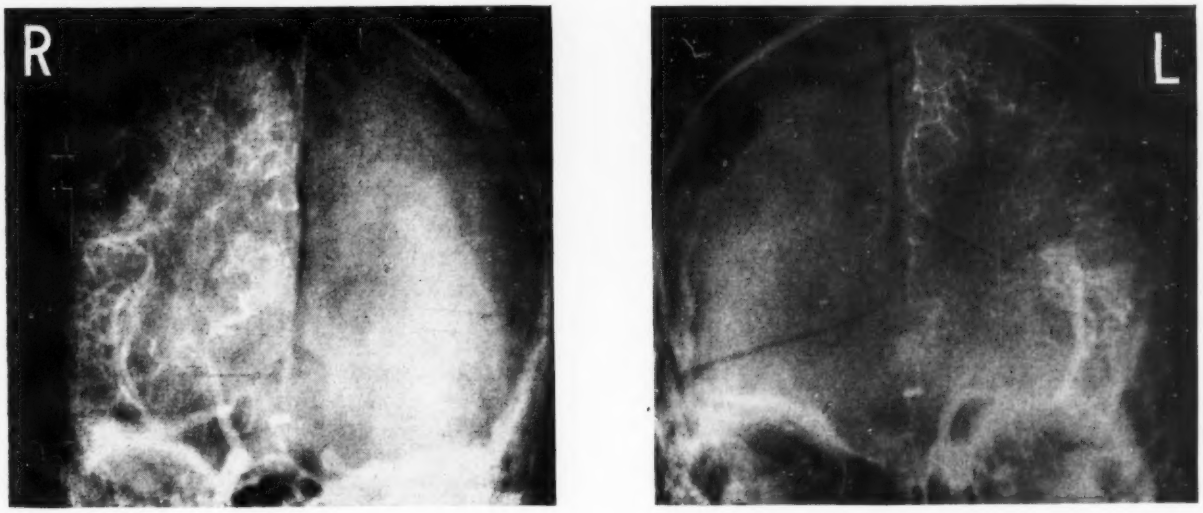


FIG. 27.—Postoperative arteriograms demonstrate silver clip in position of anterior communicating artery, and also show absence of filling of the two anterior cerebral arteries in this vicinity. Instead, the distal part of each anterior cerebral artery is being supplied by a collateral circulation from its corresponding middle cerebral artery.

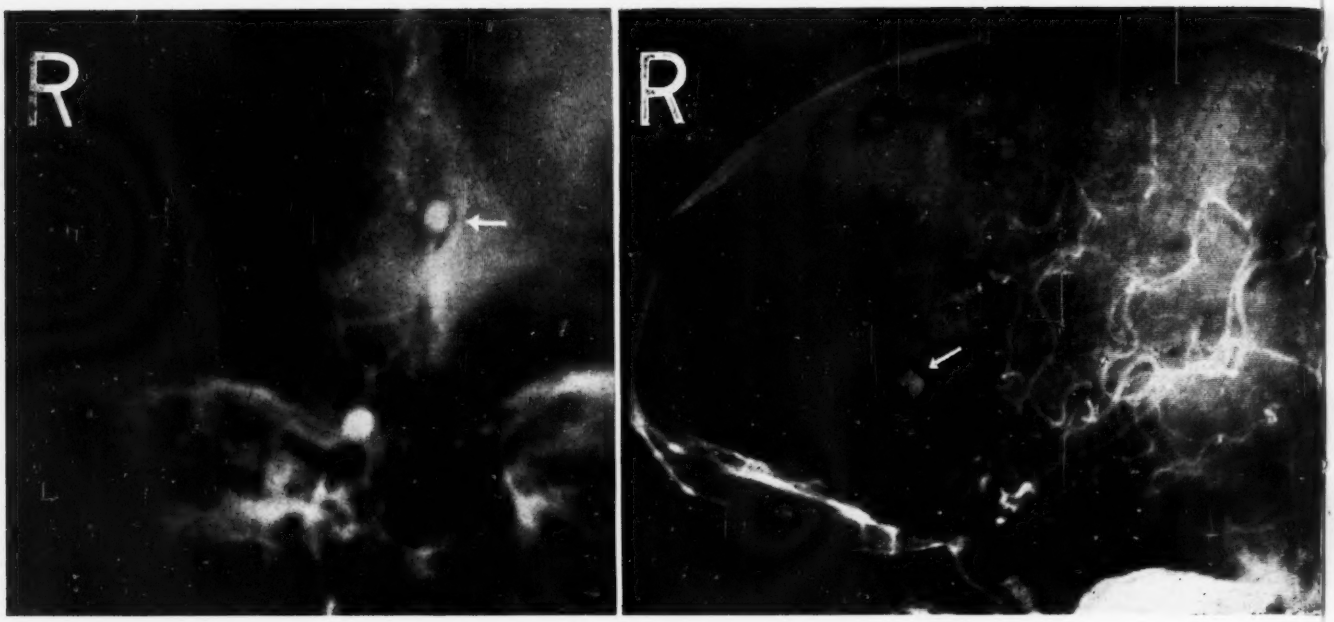


FIG. 28

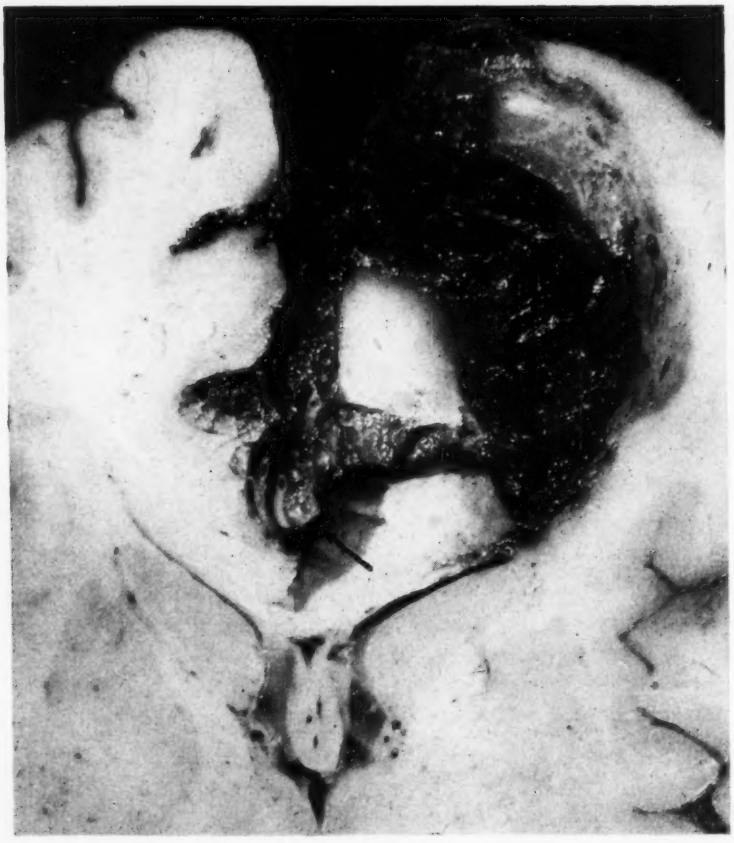


FIG. 29

FIG. 28.—Arteriogram demonstrating aneurysm arising from anterior cerebral artery at origin of its fronto-polar branch. The A.P. view shows that the aneurysm and the anterior cerebral artery are displaced slightly across the midline suggesting an intracerebral haemorrhage.

FIG. 29.—Photograph of coronal section of brain viewed from behind to show an aneurysm (arrow) of the right anterior cerebral artery associated with a haemorrhage within the frontal lobe.

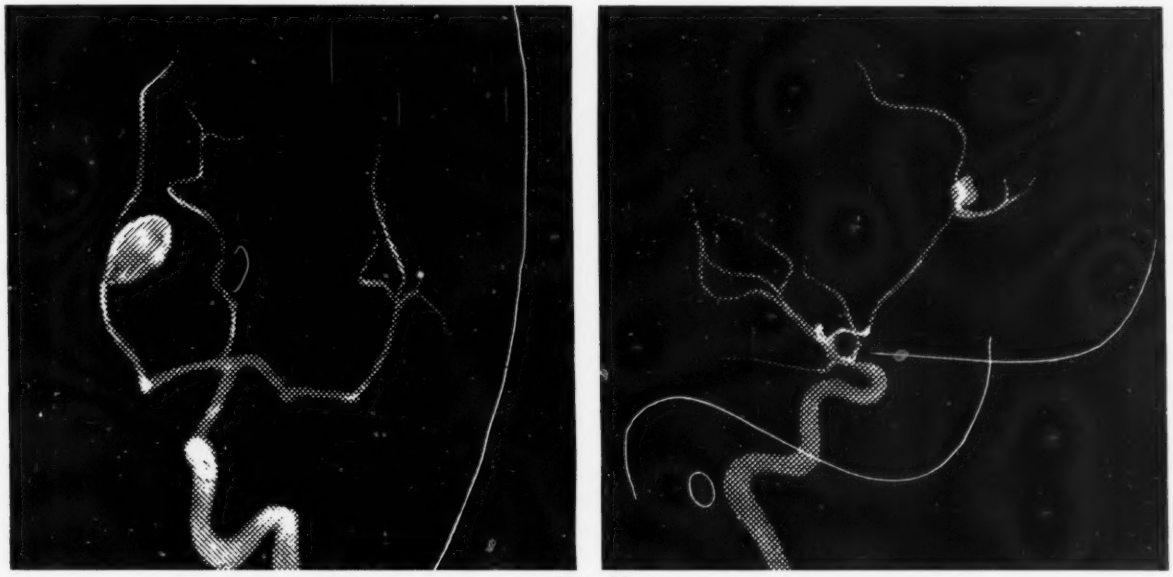


FIG. 30

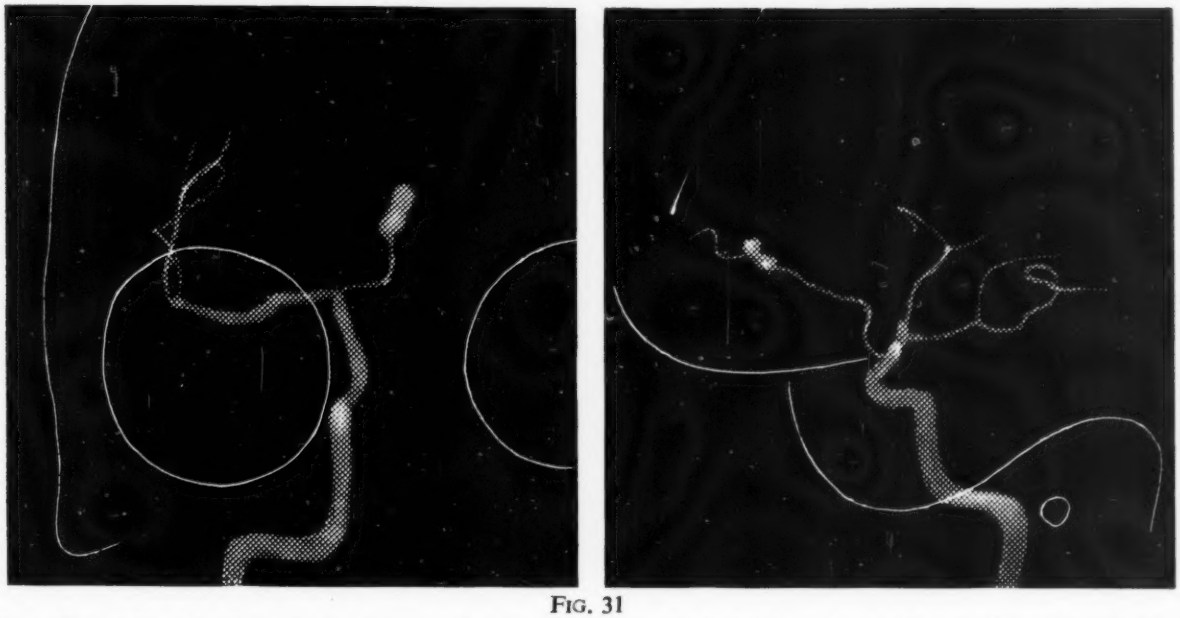


FIG. 31

FIGS. 30 and 31.—Tracings of arteriograms of other aneurysms of the distal portion of the anterior cerebral artery.

The first case ended fatally, but taught us an important lesson. The aneurysm was clearly shown by arteriography of the right carotid artery, but not of the left and there was also a shift of the anterior cerebral arteries to the left side (Fig. 28). The right common carotid artery was thereupon ligated, but the patient failed to rally, and at necropsy a large intracerebral haemorrhage was found within the right frontal lobe, the result of bleeding from the aneurysm (Fig. 29). There was no blood within the ventricles and little blood in the basal cisterns. The appearances of the brain suggested that raised intracranial pressure secondary to a large space-occupying lesion had been the cause of death, and that the proper way to have treated this case would have been by an intracranial attack.

In the two successful cases the presence of such a space-occupying lesion was recognized from the shift of the anterior cerebral artery in the arterio-

grams, and both cases were then submitted to a frontal craniotomy without resort to carotid ligation. In each instance the brain was " tight " when the dura was opened, but slackened after the convexity of the frontal lobe had been incised and the clot evacuated. In the first of these cases, one with a large aneurysm nearly an inch in diameter, there was so much scar tissue around the anterior cerebral artery in front of the aneurysm that I was not able to define the artery in this part of its course. The aneurysm was therefore buttressed with hammered muscle on the side which faced the massive intracerebral clot, while the anterior cerebral artery was exposed and clipped immediately proximal to the communicating artery. Theoretically the aneurysm should still be supplied with blood through the communicating artery, but post-operative arteriograms have not demonstrated this filling. The patient has now been followed for more than a year, and although he exhibits some impairment of initiation, he works on his own farm and has no motor disability. In the second successful case (Fig. 30) the cerebral artery was clipped on either side of the aneurysm, and the patient made an excellent recovery without any sign of motor paralysis in the leg. The post-operative arteriogram did not show filling of the anterior cerebral artery beyond the clips.

The remaining case was not really a fair test for any therapeutic procedure because the patient, although only 38 years old, had been under medical treatment for some months on account of arterial hypertension, and had a blood pressure of 215/150. Still she had had two definite attacks of subarachnoid bleeding in a month and had been unconscious since the second attack two weeks previously. The arteriograms disclosed the aneurysm, but did not fill the trunk of the anterior cerebral artery beyond it (Fig. 31). Also there was no shift, although at the subsequent craniotomy a moderate-sized haemorrhage was sucked out of the frontal lobe. At operation the aneurysm was exposed and wrapped with muscle, but following operation the patient remained mute and apathetic until her death six weeks later. At necropsy two small haemorrhages were found, one in the callosal gyrus on each side, while each anterior cerebral artery was thrombosed in its pericallosal course. This particular patient was suffering more from the general and cerebral effects of hypertensive vascular disease than from those of subarachnoid haemorrhage.

Aneurysms of the Vertebral, Basilar, and Posterior Cerebral Arteries

Most leaking aneurysms are connected with the anterior half of the circle of Willis. Richardson and Hyland (1941) in a post-mortem study of 27 ruptured aneurysms found only three ruptured aneurysms on the vertebral-basilar arterial system, while Magee (1943) in 43 ruptured aneurysms noted only nine on this system. Thus only a minority of leaking aneurysms occur on the posterior part of the circle of Willis, and very few reports of operations upon them appear in the literature. In 1944, Dandy stated : " I know of no successful outcome for operative attack upon an aneurysm in the posterior cranial fossa, but for those on the vertebral and posterior inferior cerebellar arteries, which afford good exposure, cures will certainly come in time ". Dandy also envisaged that aneurysms on the posterior cerebral artery might be attacked by resecting the occipital lobe and then clipping or thrombosing the artery on either side of its neck. German, in 1938, in a report of a single line stated that he had done this and that his patient had recovered. Since Dandy's monograph appeared Schwartz (1948) has recorded a case in which an aneurysm on a small artery in the cerebello-pontine angle was successfully treated by clipping or trapping.

No example of an aneurysm of the vertebral-basilar arterial system was recognized during life in the 69 consecutive cases of subarachnoid haemorrhage from which my 50 cases of intracranial aneurysm (all on the carotid arterial system), were collected. It is possible that there were several instances in the 14 cases in which a bleeding lesion was not demonstrated by bilateral carotid arteriography, for, in one of the two fatal cases in this subgroup, a ruptured aneurysm was found at necropsy at the bifurcation of the basilar artery. Vertebral arteriography, using King's (1942) method, was performed in only three of the cases, in each instance with normal findings, and all three patients survived. Had vertebral arteriography been performed as a routine in the nine remaining cases in which carotid arteriography was normal, it is possible that other instances of posterior aneurysm might have been disclosed. Alternatively some of the cases might have been examples of aneurysms in connexion with the anterior half of the circle of Willis, which had not filled with contrast medium either because the neck of the aneurysm was narrow or because the aneurysm had already thrombosed. Certainly Jefferson (1937), Krayenbühl (1941), Frankel (1950), and others have had experience of intracranial aneurysms that were not disclosed by arteriography, but were later found at operation. Hermann, Obrador, and Dott (1937) postulated thrombosis of the aneurysm to explain cases with normal arteriographic findings after subarachnoid haemorrhage, and we feel that, after a recent bout

of subarachnoid bleeding, the finding of normal carotid arteriograms in association with a clinical state that is improving suggests a good prognosis.

However, I have recently had a case in which an aneurysm was located on the posterior cerebral artery and was apparently successfully treated by ligation of the vertebral artery. The patient, a woman of 58 years, had three weeks earlier experienced a sudden headache followed immediately by amnesia for 10 hours with persistent headache on regaining consciousness. Ten days later she awoke with a complete palsy of the third cranial nerve on the right side. Suspecting an aneurysm of the right internal carotid artery, we obtained a right carotid arteriogram, but the appearances were normal. This was followed by arteriography of the right vertebral artery performed according to the method of Radner (1947 and 1949), and the new arteriograms disclosed an aneurysm in the position of the posterior cerebral artery close to its origin, and presumably therefore in relation to the posterior communicating artery (Fig. 32). It was also noted that the right vertebral arteriogram had shown up vessels on the right side of the cerebellum and in the right occipital lobes, but not on the left side. This was thought to indicate that the left vertebral artery was sizeable, and that the blood stream from the two vertebral arteries remained separate as they passed together up the basilar artery.

Consideration of treatment then arose. The method suggested by Dandy of resecting the right occipital lobe in order to gain access to the posterior cerebral artery would have produced a complete homonymous hemianopia, and was dismissed as too drastic. As an alternative it was felt that occlusion of the right vertebral artery would diminish the pressure and the blood-flow within the affected vessel, and so lessen the risk of further bleeding. Therefore, under local analgesia, the right vertebral artery was exposed low in the neck as it came off the first part of the subclavian artery. It was first occluded with a Crile's clamp for a period of 35 minutes and then, as there were no untoward effects, it was tied in continuity with a heavy silk ligature. The patient recovered without any anoxic symptoms, and when she was seen again three months later, her cranial nerve palsy was recovering.

Apart from German's case, about which there are no published details, this is the only case I am aware of, in which an aneurysm of the posterior cerebral artery has been treated surgically. Krayenbühl, in 1941, published particulars of a similar case also with a unilateral third nerve palsy in which by means of vertebral arteriography (Moniz method) he had demonstrated an aneurysm in the same situation on the posterior cerebral artery. The aneurysm, however, was not treated surgically.

The procedure of vertebral ligation should be approached warily. Dandy (1944) stated that he had ligated one vertebral artery " perhaps 20 times without any untoward effect ", and also quoted Alexander who, in 1882, had reported having ligated with impunity one or even both vertebral arteries as a treatment for epilepsy. However, recently both Guthkelch (1949) and French and Haines (1950) have reported cases where a fatality followed ligation of one vertebral artery. Dandy also gave his personal experience of a case in which, after having occluded one vertebral artery, he prepared the second for ligation. " Before the vessel was ligated it was compressed with the forceps for perhaps two seconds and then released. Death was immediate. Pulse and respiration ceased, and despite release of the compression and artificial respiration there was no return of pulse or breathing. There could be no more speedy death."

DISCUSSION

Statistics are not available by which one can precisely measure the mortality rate that would have occurred in our 50 cases of leaking aneurysm had they not been treated surgically. There are, however, certain pointers. First, in the ordinary run of cases of spontaneous subarachnoid haemorrhage the mortality rate varies between 50 and 60% with a satisfactory recovery rate of between 16 and 30% (Table I). Secondly, in cases that develop recurrent bleeding the mortality rises even higher (Table II). And thirdly, when cases of subarachnoid haemorrhage die and come to necropsy, ruptured aneurysms can be demonstrated in about 75 to 80% (Richardson and Hyland, 1941 ; Magee, 1943 ; Hyland, 1950). As my series contained so many recurrent cases, I think it can be conceded that the mortality likely in our 50 cases of aneurysm, had they continued on conservative treatment, would have been even higher than the average figures mentioned above.

Instead, my series of operated cases shows a mortality rate of 18% associated with a satisfactory recovery rate of 66% and a total recovery rate of 82%. In addition, five of the disabled female patients, although exhibiting an appreciable degree of paralysis, are still able to look after their homes with little or no assistance from others, and these, if added to the good recoveries, make a useful recovery rate of 76%. Only three of the surviving patients (6% of total group) are severely disabled. Furthermore, of the 24 patients in my series, whose ages were 40 years or less, only two died (mortality rate 8·5%), whereas in a comparable group of 141 patients in the same age groups with spontaneous

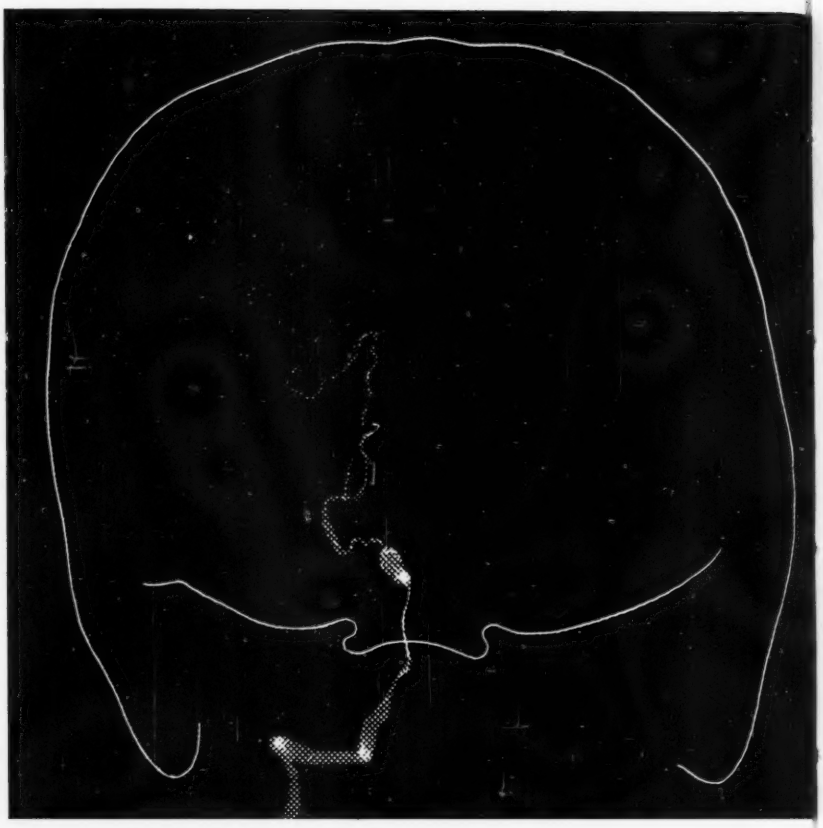


FIG. 32.—Tracings of arteriogram of vertebral artery showing an aneurysm of the posterior cerebral artery.

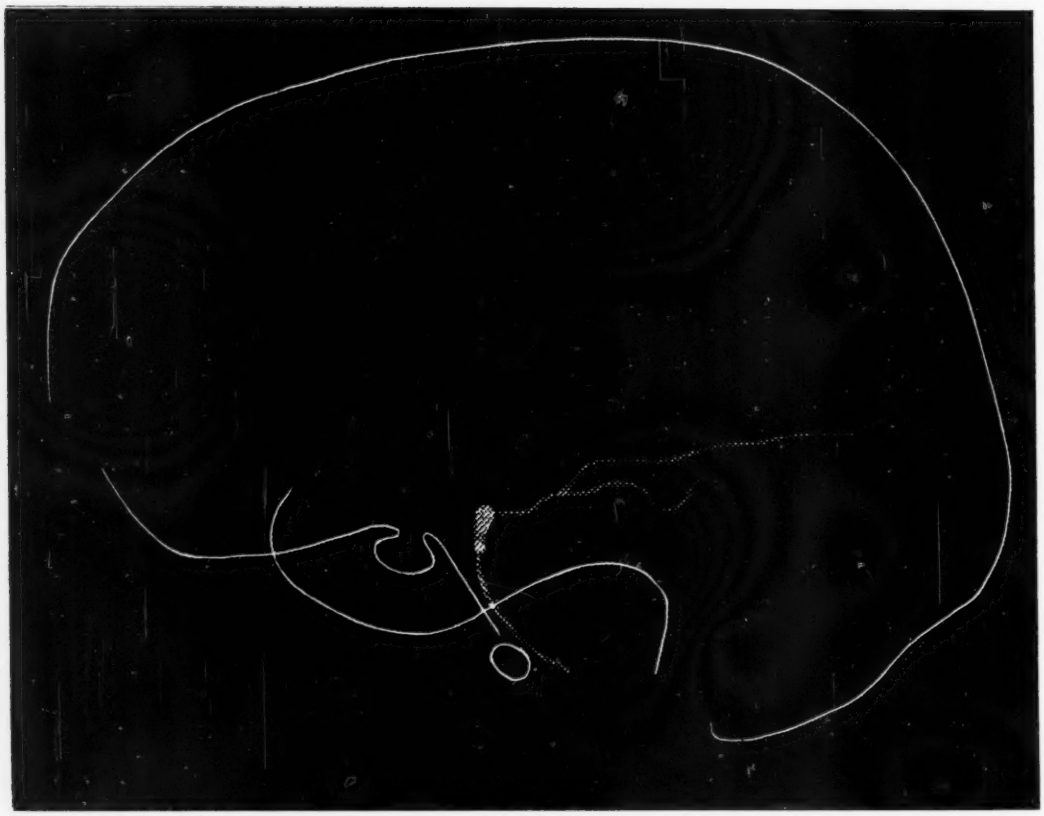


TABLE I

MORTALITY AND RECOVERY RATES* WITH CONSERVATIVE TREATMENT IN SPONTANEOUS SUBARACHNOID HAEMORRHAGE

	Birmingham Hospitals, U.K. (Taylor and Whitfield, 1936)	Buffalo General Hospital, U.S.A. (Hamby, 1948)	Dunedin Hospital N.Z. (Author's data, 1943–47)	Toronto General Hospital, Canada (Hyland, 1950)	Ministry of Pensions, U.K. (Magee, 1943)
Number of patients	81	130	31	191	150
Died while under treatment (%) ..	60	63	55	53	56
Recovered satisfactorily (%) ..	? Under 20	16	19	?	30

* The statistics of Wolf, Goodall, and Wolff (1945) relating to the New York Hospital are more favourable than those listed above, but have been excluded because some selection evidently occurred in their case-material.

TABLE II

PROGNOSIS WITH CONSERVATIVE MANAGEMENT OF PATIENTS IN INITIAL AND RECURRENT ATTACKS OF SUBARACHNOID HAEMORRHAGE

	Buffalo General Hospital, U.S.A. (Hamby, 1948)	Dunedin Hospital, New Zealand (Author's data, 1943–47)	Ministry of Pensions, United Kingdom (Magee, 1943)
Number of patients observed in initial attack ..	98	31	150
Proportion who died in initial attack	? 42%	23%	35%
Number of above patients who survived initial attack	—	24	98
Proportion of these who developed a recurrent attack while under observation	—	46%	51%
Number of patients who developed a recurrent attack while under observation	61	11	50
Proportion of these who died in recurrent attack ..	65%	91%	64%

subarachnoid haemorrhage treated conservatively, Magee (1943) found that 79 died (mortality rate, 56%). This improvement in prospects for patients treated surgically has led us to the conclusion that surgical treatment should become a routine measure in the treatment of subarachnoid haemorrhage when the vascular abnormality or aneurysm can be located by arteriography.

My patients have now been followed up for periods ranging between six months and four years, and so far only one instance of recurrent haemorrhage has been reported. This recurrence occurred within four weeks of operation and is discussed in an earlier section, while the case itself is included in the total of fatal cases. It is possible that recurrent bleeding may yet arise in other cases, either from the aneurysm which was treated or from a fresh aneurysm, but the proportion of recurrences is not likely to be large. In contrast Hyland (1950) records that of 67 patients who were traced for an average period of 10 years following recovery under a conservative regime, recurrent haemorrhage was found to have occurred in about 20%.

Nine patients in the series died, and eight recovered with an appreciable disability. In the light of later experience these results might have been improved, had some of the patients been handled differently. Certainly two patients died primarily because of space-occupying effects of large intracerebral clots which should have been removed. One patient died of infarction of both frontal lobes because we had unwittingly tied an internal carotid artery which was supplying both anterior cerebral arteries. Further, in three cases the application of a silver clip to the neck of the sac caused the sac to burst and, although the haemorrhage was controlled at the time by other means, all three cases subsequently developed spreading thrombosis and two of them died. Thus, although we had some success with this method we have now become very chary of applying it. The outcome in all these cases just cited might

have been bettered, but in those other cases which died from laceration and infarction of the adjacent brain from intracerebral haemorrhage death might not have been preventable.

The question then arises as to how soon after an attack of subarachnoid haemorrhage should one wait before beginning surgical investigations. Our policy now is to do this as soon as arrangements can conveniently be made, no matter whether the patient has had one or several bouts of bleeding or whether bleeding is still in progress or has stopped. If a patient is still actively bleeding, and his transfer involves long road or air transport, we prefer to wait 24 hours or so until the fresh bleeding ceases, before transporting him to the neurosurgical centre.

There is in subarachnoid haemorrhage a marked tendency towards recurrence of bleeding. Indeed of those patients who survive their first attack half will develop a recurrence of bleeding (Table II), and, as Magee (1943) has also shown, the incidence of these recurrences reaches its peak in the third and fourth weeks after the initial attack, at a period when the patient seems to be progressing favourably (Table III). It is therefore wise not to procrastinate

TABLE III

LATENT PERIOD BEFORE RECURRENCE IN PATIENTS SURVIVING INITIAL ATTACK OF SUBARACHNOID HAEMORRHAGE*

(1) Total cases of subarachnoid haemorrhage ..	150
(2) Died of initial attack	52
(3) Survived initial attack but developed a recurrent attack	50

Analysis of Subgroup (3)

Period within which bleeding recurred (Weeks)	Cases	Died
1	4	3
2	9	5
3	12	8
4	7	7
5	4	1
6	4	2
7	3	1
8	0	0
Over 8	7	5
	50	32

* From Magee, 1943.

with the decision to perform arteriography. We learnt this partly by experiences additional to those already mentioned. During the period when we were collecting our first 12 cases, our medical colleagues asked us to see in consultation five patients admitted to their wards shortly after their first attack. By the time we saw them they seemed to be settling nicely, and so we decided to leave them alone. But to our later regret no fewer than three of them subsequently developed a second attack while still in hospital and all three succumbed rapidly before we could be advised. At necropsy each case exhibited what would have been a surgically remediable lesion. This experience greatly influenced our attitude to subarachnoid haemorrhage, and subsequently we have regarded all cases of this condition as surgical emergencies. In only two cases of subarachnoid haemorrhage referred to us since then have we failed to undertake surgical treatment, and then only because the patient was moribund and died before we could begin. The temptation to leave a patient alone because he appears to be settling spontaneously is clearly a dangerous policy to adopt.

Not all cases of subarachnoid haemorrhage are due to intracranial aneurysms, although the majority are. As has already been pointed out, during the period in which we collected these 50 cases of aneurysm, we also saw 19 other cases with subarachnoid haemorrhage, four of which were found to be due to leaking arteriovenous malformations, one to a tiny perforation on a major vessel without aneurysmal formation, while in the remaining 14 cases no arteriographic abnormalities were seen. The four cases of leaking arteriovenous malformation as well as the one with a perforation were all operated on with recovery, while of the 14 cases in which no arteriographic abnormality was seen and hence no definite surgical procedure carried out, only two died. The total mortality for the whole group of 69 cases was 11 deaths, or 16%. Surgery, therefore, has a place in the treatment of subarachnoid haemorrhage as a whole, and not merely in the cases due to aneurysm.

The surgery of intracranial aneurysms is still in its infancy and we have come a long way since Harvey Cushing (1923) described cerebral aneurysm as " a lesion having such remote surgical bearings ". Further developments are likely. The demand for surgery will probably grow appreciably, for subarachnoid haemorrhage is relatively common. In New Zealand we arrived at statistics which suggest that in that country one case of subarachnoid haemorrhage occurs per 10,000 of population each year (Falconer, 1950), while elsewhere pathologists have observed an incidence of cerebral aneurysms in from 0·5 to 1·5% of persons who come to necropsy (Richardson and Hyland, 1941). The field for surgery is thus a large one. It is also a rewarding one, for the patients are often young and active subjects whose misfortune is merely that they have " a length of defective tubing " in their blood vessels, which, if repaired, will ensure their full and active lives once more. They are a more rewarding group than are the intracranial tumours with which

neurosurgeons so largely concern themselves. We have demonstrated that they can be benefited surgically, but the methods which we applied may with further experience be improved upon. Other surgeons doubtless will try other measures, and time will decide their permanence and worth.

SUMMARY

A series of 50 consecutive cases of leaking intracranial aneurysm was treated surgically by carotid ligation or an intracranial exposure, or by a combination of these procedures, with nine deaths. Thirty-three patients made good recoveries; five patients, although disabled, are leading economically useful lives, and three patients are severely disabled. These figures are compared with the mortality rate of between 50 and 60% and the satisfactory recovery rate of between 16 and 30% which follows conservative management in the ordinary run of cases of subarachnoid haemorrhage. Probably the mortality rate in the surgical series, had they not been submitted to operation, would have been higher than these figures.

It is felt that all cases of subarachnoid haemorrhage should be submitted as soon as possible to carotid arteriography, and that those cases in which an aneurysm or arteriovenous malformation is revealed should be operated on forthwith.

The treatment of choice for aneurysms of the intracranial internal carotid artery is felt to be stage-ligation of the common carotid artery, followed later by ligation of the internal carotid artery in the neck and by clipping of the intracranial internal carotid above the neck of the aneurysm and below the neck of Willis (i.e. trapping of the aneurysm).

The treatment of choice for aneurysms at the bifurcation of the internal carotid artery is a direct intracranial exposure and either wrapping the aneurysm with muscle or clipping its neck. This may be preceded by a preliminary carotid ligation.

The treatment of choice for aneurysms of the middle cerebral artery or of the proximal part of the anterior cerebral artery including the communicating artery is also by a direct intracranial exposure with wrapping of muscle around the aneurysm. Clipping the neck is sometimes efficacious, but carries the risk of operatively rupturing the aneurysm. These aneurysms are often associated with haemorrhage into the adjacent frontal or temporal lobes, and such intracerebral clots should be evacuated. In some cases a preliminary carotid ligation is required.

For aneurysms of the anterior cerebral artery distal to the communicating artery, trapping the aneurysm between clips or ligatures placed on the parent artery is felt to be a practical method. Carotid ligation is not required.

A single case of aneurysm of the posterior cerebral artery causing both subarachnoid haemorrhage and one isolated third nerve palsy is reported. It was treated by unilateral vertebral artery ligation.

It is felt that spontaneous subarachnoid haemorrhage is an emergency which calls for surgical handling.

My thanks are due to the various physicians and surgeons who have entrusted their patients to me, and in particular to Professor F. G. Bell, F.R.C.S., Dr. J. A. D. Iverach, and Dr. R. H. Q. Baxter, who encouraged me in my first operations. My former associate, Mr. Anthony James, F.R.A.C.S., now head of the Dunedin Neurosurgical Unit, collaborated in the operative work, and Dr. A. C. Begg and Mr. M. Allen of the *x*-ray department of the Dunedin Hospital contributed in the arteriographic studies. Mr. James also furnished the operation sketches, and Miss Treadgold, of the Department of Medical Illustration, Guy's Hospital, made the arteriographic tracings. I am indebted to Sir Charles Symonds, K.B.E., for helpful criticisms regarding the assembling of this paper.

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SENSORY DISTURBANCES IN CORTICAL WOUNDS WITH SPECIAL REFERENCE TO PAIN

BY

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The role of the cortex in the appreciation of the various forms of sensation has been of interest to neurologists for many years. Towards the latter part of the nineteenth century a vast amount of work on the functions of the cerebral cortex was done by clinical workers and by the experimental physiologists. From these studies there emerged three schools of thought. The first was mainly represented by Ferrier (1886), who, from his observations on the effect of extirpation of the cortex in the experimental animal, concluded " that the thus produced affection is a purely motor one, and the centres or regions in question are strictly motor ". Schäfer (1898) took a similar view.

The second school supported by Munk (1892) and Mott (1894) maintained that the Rolandic area was primarily sensory, and registered impressions occasioned by movements. The last view was that originally proposed by Hughlings Jackson, and adopted by Horsley in his Linacre Lecture of 1909, namely, that the Rolandic region was in reality sensori-motor. The difficulties which prevented the reconciliation of these various schools were many, not the least being confusion with regard to the terms used. Campbell's classical work in 1905 clarified the situation by demonstrating that the pre- and post-central convolutions differed in structure, a point already illustrated by Birt (1904), when he described a circumscribed lesion of the post-central convolution with no impairment of motor function.

Though the main concern of the observers of this period was with tactile sensibility the problem of the localization of pain sensibility was not ignored. Hitzig (1900) stated categorically that pain sensation was formed subcortically. On the other hand, Russel and Horsley (1906) reported a case of pachymeningitis of the cortex in which the cortex was excised posterior to the fissure of Rolando to a depth of 2 cm. This patient showed marked analgesia and loss of temperature sense. Three years later Horsley (1909) said :

> " The evidence I possess on the question would seem to show that the conscious appreciation of pain in the upper limb is partly represented in the post-central gyrus. After free removal or destruction of the whole arm centre—that is both central gyri—it is notably diminished, though like all forms of sensation not totally abolished."

So by the end of the first decade of this century the present conception of the post-central gyrus as the great sensory projection area had been evolved. The next year but one after this publication marked the appearance of the classical studies of Head and Holmes (1911) which will form the basis of the subsequent discussion. They considered that the thalamus has two functional parts. There is first a receptive centre in the lateral nucleus where all sensory fibres terminate. From here fibres are divided into two major groups, the one subserving position sense and discriminative forms of sensibility which are passed on directly to the cortex, the other subserving pain, heat, cold, and gross touch which are relayed to the grey matter of the thalamus to a physiological station which they termed the essential organ of the thalamus. Here the effects of these impulses enter consciousness. Though they have no representation in the cerebral cortex, they are not entirely free from cerebral control, however, for in the normal person the response to pain does not have the excessive, explosive character of those with thalamic lesions. This is due to the exercise of cortical control which conditions the thalamic response just as Head (1920) visualized epicritic sensation to control the response to protopathic forms of sensibility. In thalamic lesions, however, the control is removed and the excessive response to unpleasant stimuli becomes manifest.

There are, however, many difficulties inherent in this hypothesis. Objection was raised that if the

thalamic over-response was due to loss of cortical control, it should equally appear in cortical lesions which remove the source of this control. This objection was met by the supposition that, as fibres come from all parts of the cortex to the thalamus, the lesion must be situated near their end point in order to remove completely cortical control. Interruption of a portion of the fibres only, as must occur in a cortical lesion, was insufficient to permit the thalamus to manifest itself in its uninhibited state. Further, since they believed that this altered pain sensation was entering consciousness in the thalamus, it followed that the receptor centre and the essential organ must be intact, or at least largely so. No such anatomical divisions as the receptor centre and the essential organ have been demonstrated. Hence we are asked to visualize a lesion in the lateral part of the thalamus which cuts thalamo-cortical fibres completely but spares the fibres from the fillets entering the thalamus and the cell stations comprising the " essential organ ". Any attempt to establish the medial nucleus of the thalamus as a discrete " essential organ " for pain sensibility was prevented by the observation of Smyth and Stern (1938) that lesions confined to this part of the thalamus produced no sensory changes at all.

A further blow was struck by the work of Le Gros Clark (1932) who showed that when the cortex is removed there follows complete degeneration of the grey matter of the lateral part of the thalamus. As has already been pointed out, Head and Holmes maintained that all cortical fibres must be cut to enable the thalamic syndrome to appear. Where then, when complete degeneration of the cells of the thalamus has occurred, lies the essential organ ? Despite these weighty objections it became generally accepted and a part of classical neurological belief that sensibility to pain, heat, cold, and gross touch are not represented in the cortex but have their end station in the thalamus where these forms of sensation enter consciousness. Yet a more careful perusal of the later works of Head and Holmes raises the suspicion that perhaps they did not feel the conviction on this matter that their work appears to have carried.

These doubts are plainly manifest in *Studies in Neurology* (Head, 1920). Thus he wrote (page 665) :

> " But, although, the appeal of all such aspects of sensibility (pain) is overwhelmingly thalamic it must not be forgotten that pain can be roughly graded according to the intensity of the stimulus ; in so far, it is the product of cortical activity."

And later in summarizing his section on the " measured prick " :

> " Thus we can sum up as follows our present experience of the effect produced by a cerebral injury upon sensations of pricking.
>
> (1) A gross subcortical lesion tends to raise the threshold to measured pricks distinctly, but not to an extreme degree.
>
> (2) Injury to the cortex, uncomplicated by destruction of subcortical tissues, does not tend to raise the threshold materially. But it may produce a profound difference in character of the sensation ; this is due, in great part, to disturbance of that aspect of discrimination sometimes called the ' sense of a point'.
>
> (3) Cortical activity, however, probably exercises a distinct influence even over the appreciation of the relative intensity of successive pricks. But this is so slight that it was not measurable in most of the cases of injury extending over a comparatively small area which formed the basis of this research."

The difficulty of this question as to whether pain sensibility can be abolished or even profoundly affected by cortical lesions is manifest by the fact that German observers were taking an entirely opposed view at this time. The best account of these is undoubtedly contained in the work of Kleist (1922). His conclusions were based on observations made on head wounds of the 1914–18 war, and he postulated that pain and temperature sensation are represented in the front part of the post-central convolution. A further observation was that not only could pain and temperature be decreased but that an excessive response could appear, as a result of a cortical lesion. He found that in these cases there is usually associated diminution of position sense, discrimination and localization, and, therefore, he supposed that while the areas for these latter forms of sensibility were destroyed the neighbouring areas for pain and temperature were being irritated. Moreover he discovered that this response to the pin-prick in these cases had lost its pointed nature and was diffuse and unpleasant, and he suggested that the release of this so-called protopathic form of sensibility of Head (1920) could occur in central as well as in peripheral lesions.

Nor were the Germans alone in this viewpoint, for the French school was taking a similar view. As early as 1915 Dejerine and Mouzon reported the case of a lieutenant with a small cortical wound and loss of pain sensibility in the contralateral arm. Then in 1923 Piéron published his book, *Le cerveau et la pensée* in which he reviewed French wartime experiences with cortical wounds. He attributed to various forms of sensation a coefficient running from 1, which was normal, to 5, which indicated complete loss of that form of sensibility. His list of mean coefficients of the observations collected were :—

Superficial touch ..	3·60
Deep pressure	3·54

Heat and cold	3·21
Pain	3·35
Vibration through bone	3·47
Appreciation of weight	3·75
Tactile discrimination ..	3·80
Tactile localization ..	3·38
Position	4·00
Stereognosis	4·13

From this he considered that pain sensibility could be affected by cortical wounds. Later in 1932 Guillain and Bertrand quoted the case of a woman aged 53 years, who besides experiencing spontaneous pains had hypoalgesia over the right side of the body. Post-mortem examination revealed bilateral parieto-occipital lesions, and the authors state categorically that the thalamus was not involved.

Kinnier Wilson (1927) drew attention to evidence that pain has a definite representation in the human cortex and that previous conclusions in the opposite sense must be reconsidered. Michelsen (1943) and Earl Walker (1943) held the same view. Davison and Schick (1935) described two cases of cerebral embolism with resultant softening of the post-central and parietal convolutions. The patients had hypoalgesia and hyperpathia on the contralateral side, and careful necropsy studies established that the thalamus was not involved.

Pain as an aura in epilepsy was described as early as 1901 by Gowers in his book, *Epilepsy and Other Chronic Convulsive Disorders*, and has frequently been considered to favour the thesis that pain is represented in the cortex. Souques (1921) described a woman aged 23 years who had epileptic attacks beginning with severe pain in the left hand, and was found to have a psammoma lying over the right Rolandic cortex. Also Holmes (1927a) in discussing a case of left-sided sensory epilepsy wrote :

> " The attacks always began with tingling in the left arm sometimes so intense as to be actually painful, and then spread slowly to the shoulder down the trunk and into the left leg."

It might have been thought that the development of electrical stimulation of the cortex in the conscious human subject as a method of investigation might have thrown light on the representation of pain in the cortex. Foerster stimulated the post-central gyrus electrically and noted contralateral pain. Cushing (1909), however, stimulated the post-central gyrus in two patients but no pain was caused. Penfield and Gage (1933) on the other hand, reported two cases of pain following electrical stimulation of the cortex.

Later Penfield and Boldrey (1937) described further instances of pain following cortical stimulation, but wrote :

> " The fact that only eleven times out of well over eight hundred responses did the patient use the word pain to describe a cortical sensation probably indicates that pain has little if any true cortical representation."

Some interesting observations on sensory disorders following cortical wounds have also been reported by Russell (1945). He found two groups of cases in post-Rolandic wounds. Those examples in which the main incidence of the damage was thought to be on the posterior bank of the central fissure—area 3 of Brodmann—suffered loss of the primary forms of sensation, namely, pain, temperature, and touch as well as the discriminative forms. The group of wounds apparently situated on the lateral aspect of the post-central convolution (areas 1 and 2), in contrast, suffered permanent loss of the discriminative forms only. He described also examples of hyperpathia in wounds confined to the cortex. He stressed, however, the difficulty of reconciling these findings with the well known fact that in gross lesions of the sensory and motor cortex, pain sensibility is usually well preserved. He wrote :

> " We thus come to the apparently paradoxical finding that while limited wounds of the Rolandic area often cause permanent loss of all forms of sensation in a contralateral limb, gross injuries to the same area permanently destroy discriminative sensory functions only."

Finally the results of animal experiment, though obviously inferior to human observations, should be mentioned. In 1944 Peele reported the results of acute and chronic cortical ablations in monkeys. He found that the response to pain stimuli was impaired or absent, following ablation mainly of area 3, for a period of three weeks. In one experiment where the whole of the parietal cortex, except area 3, was removed there was hyperpathia lasting at least eight months.

Material and Methods

The material for the present work has been studied almost exclusively at the Head Injury Advice Bureau at a military hospital for head injuries, and consists of 1,000 cases of penetrating brain wounds. Amongst these, 186 cases with permanent sensory loss were found, and 43 were re-examined personally. Many of these have been excluded because of extensive wounds or frequent fits.

The 18 cases reported here have been divided into four series. From the records 25 cases of cortical wounds with impairment of pain sense were found, and of these it was possible to re-examine 10. In addition one case (Case 10) of a penetrating wound of the 1914–18 war under the care of Dr. Ritchie Russell has been included. These 11 cases comprise Series A.

Series B consists of two examples of persistent hyperpathia following cortical injury. Records of

eight cases in all were found, but it was only possible to examine personally three of these. Series C contains two instances of dissociation between pain and temperature sense resulting from cortical wounds, and the records of six more examples were studied. Finally, Series D is made up of two examples of more extensive brain wounds in which position sense and 2-point discrimination were lost but pain was preserved.

One additional case (Case 18), a patient of Dr. Fergus Ferguson, has been included. This patient had pain loss due to a cortical neoplasm and has been reported to exemplify the superiority of traumatic material over neoplastic in studies of this kind. This material is summarized in Table I.

TABLE I

SUMMARY OF TYPES OF CASES IN PRESENT SERIES

Series		No. of Cases
A	Cortical wounds with pain impairment	11
B	Cortical wounds with hyperpathia	2
C	Cortical wounds with impairment of temperature sense but pain preserved	2
D	Extensive wounds with loss of discriminative sensibility but pain preserved	2
–	Case of cortical neoplasm with pain loss	1
	Total	18

Method of Examination.—Each patient had first a routine neurological examination with special attention to the integrity of the visual fields because of its value as evidence of the superficial nature of the wound. The following modalities of sensation were then tested, sense of position and passive movement, 2-point discrimination, light touch, vibration, sensibility to pin-prick, temperature sense, and finally deep pain.

The senses of position and passive movement were tested by fixing the limb or digit above the joint to be tested with one hand and holding the part distal to the joint firmly at the sides with the other hand. The joint was then moved gently through the required range of movement. The angles of movement employed were 5° and multiples thereof.

2-Point discrimination was tested with a pair of dividers applied simultaneously, in the case of both points, to the skin. The distance separating the points was measured accurately on a ruler and differences of 0·1 cm. were noted.

Vibration sense was tested with a C 128 tuning fork. The instrument was applied to the defective side, and when the patient ceased to feel it, was immediately transferred to the opposite limb and the duration of vibration on that side was noted.

Light touch was tested with light and heavy threads of nylon, which for purposes of this study are referred to as No. 1 and No. 2 respectively, with a wisp of cotton wool, and where necessary with a light touch of the finger. The skin was touched with these objects and they were not drawn along the surface. The results are recorded as the number of stimuli appreciated out of each ten stimuli.

Pin-prick was tested with an ordinary pin, but thrusts were heavy to ensure it was pain that was tested and not the sense of point. Testing colleagues has shown that in practice a constant degree of pain can be achieved by the ordinary clinical method of testing with a pin. The results were recorded as being of two grades. " Lost " was recorded when even on penetrating the epidermis the patient felt no pain but was only aware of a touch. " Gross impairment " was recorded when the patient felt slight pain on pushing a pin through the skin.

Temperature sense was tested with water in metal tubes with a thermometer to record the temperature. The patient was asked to differentiate between tubes of different temperatures applied successively to an area. In addition the same tube was applied to comparative areas on both sides of the body and the patient was asked to say if they felt the same or differently.

All the deep pain tests were made by the method employed by Kellgren (1938a) in his studies on pain arising from deep structures. An injection of 0·2 ml. of 6% sodium chloride was made into muscles. A preliminary testing was usually carried out by a pressure algesiometer in order to obtain some idea of the extent of the analgesic areas, as it was found advantageous to test these areas first with the hypertonic saline as the enthusiasm of the patient tended to wane rapidly when normal areas were injected.

Case Records

Series A.—This consisted of patients with small cortical wounds with pain impairment.

Case No. 1 (*No.* 10813).—This man was wounded on January 23, 1945, in the right parietal region by a sniper's bullet. He did not lose consciousness and remembers that his left arm immediately became numb and powerless. He was examined at No. 6 M.N.S.U. by Capt. P. L. M. Hartley within 24 hours. The patient was conscious and quite rational. There was a faint trace of left facial weakness. In the left arm there was complete loss of power and loss of all modalities of sensation. The legs were normal and plantar responses were flexor. He was operated upon on January 25 by Capt. J. W. Turner. There was a small depressed fracture in the right parietal region which was elevated. The dura was intact though tense, but it was not blue. The dura was left intact, and the wound excised and cleaned (Fig. 1). He was examined by Dr. G. E. Smyth on March 28, 1945. There was then deep hypalgesia of the whole of the left face with hypaesthesia also. The facial weakness was hardly discernible. The power

at the shoulder and elbow was 60% but in the fingers there was only a flicker of movement. On the sensory side there was hypoalgesia of the whole of the left arm with hypaesthesia and loss of temperature sense, likewise of postural sense, 2-point, vibration, and stereognosis.

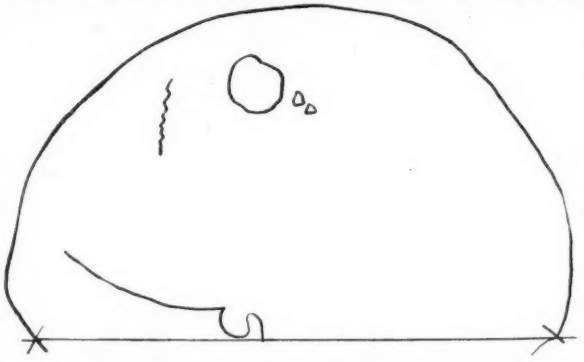

FIG. 1.—Tracing of lateral radiograph of skull showing site of wound in Case 1.

I examined him five years later on August 24, 1950. He was at work and had no fits. Visual fields were full and the cranial nerves were normal. The weakness and sensory disturbance in the face were no longer detectable. Reflexes in the left arm were increased with slight hypertonus. Power in the shoulder and elbow was still only 60% and only a flicker of movement was present in the fingers. The legs were normal. The sensory findings were :—

Right Arm	Left Arm
Position and Passive Movement	
Fingers 5° correct	90° failed
Wrist 5° correct	30° direction correct
Elbow 5° correct	5° correct
Vibration Normal	Lost
2-point	
Fingers 0·3 cm.	No threshold
Touch (No. 1 nylon)	
Fingers 10/10	0/10
Forearm 10/10	5/10
Arm 10/10	10/10
Pin-prick Normal	Lost left hand; gross impairment left forearm
Temperature	
22°–33° : 24°–40°C Resolved	Not resolved

Deep Pain

0·2 ml. of 6% sodium chloride was injected into identical sites of both arms. No pain was felt on the left and severe pain on the right.

Case No. 2 (*No.* 9683).—This man sustained a penetrating wound in the right parietal region on August 22, 1944, with momentary loss of consciousness. He was examined the next day by Capt. J. H. Paterson at No. 6 M.N.S.U. The visual fields were full but there was weakness and loss of sensation over the left side of the face. There was considerable weakness with increase of tone and reflexes in the left arm. The leg was normal and the left plantar response equivocal. All modalities of sensation were reported lost on the left arm and neck. He was operated on by Major C. A. Calvert on August 25, 1944. There was a large dural tear and a track 3 cm. deep containing clot (Fig. 2). The last recorded examination was made on November 7, 1944. There was greatly diminished power in the left arm with slight impairment in the leg. Reflexes were normal and plantars were flexor. Position sense and stereognosis were lost on the left, and there was hypoaesthesia and analgesia of the whole of the left side maximal in the arm and least in the foot.

I examined him on February 6, 1950. He was well and at work. Since 1946, however, he had experienced occasional attacks of loss of consciousness for a minute without convulsion. The last attack had been three months before examination. There was decreased power and increase of tone in the left arm and less so in the left leg. The reflexes and plantar responses were normal and the fields of vision were full. Sensory findings were :—

Right Arm	Left Arm
Position and Passive Movement	
Fingers 5° correct	90° movement only
Elbow 5° correct	60° movement only
Vibration Normal	Greatly diminished
2-point	
Fingers 0·4 cm.	No threshold
Touch (wool) 10/10	1/10 2/10
Pin-prick Normal	Gross impairment
Temperature Normal	Differences of 4°C resolve accurately

Right Leg	Left Leg
Position and Passive Movement	
Toes 5° correct	90° movement only
Vibration Normal	Greatly diminished
Touch (wool) Normal	2/10
Pin-prick Normal	Gross impairment
Temperature Normal	Resolved differences of 4°C slowly

Deep Pain

0·2 ml. of 6% sodium chloride was injected into identical sites of both arms and legs. No pain on the left but severe pain on the right. 0·1 ml. of 6% sodium chloride into left masseter did produce pain in area of upper molars but it was not so severe as on the right.

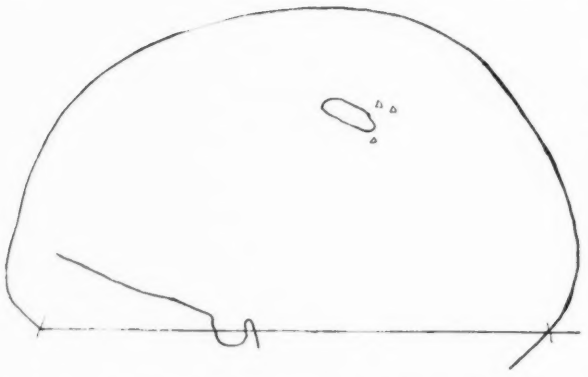

FIG. 2.—Tracing of lateral radiograph of skull showing site of wound in Case 2.

Case No. 3 (*No.* 10386).—This man sustained a parasagittal gunshot wound on October 26, 1944. He was unconscious for less than a minute, after which he found he could not move his left leg. He was examined some ten hours later at No. 9 British General Hospital, when both legs were found to be spastic with increased reflexes and extensor plantar responses. The left leg was extremely weak, the right leg slightly so. Postural sense was impaired in both feet, and there was hypoaesthesia of the left leg up to the level of the mid-thigh. He was operated on the following day by Lt. A. E. James. The skull was abraded, but there was no fracture. The wound was excised and closed in layers. He was examined by Dr. W. Ritchie Russell and Dr. G. E. Smyth in March, 1945. There was noted to be severe impairment of position and vibration sense in the left leg with hypoaesthesia and hypoalgesia up to mid-thigh. Pressure pain appeared to be absent in the left leg.

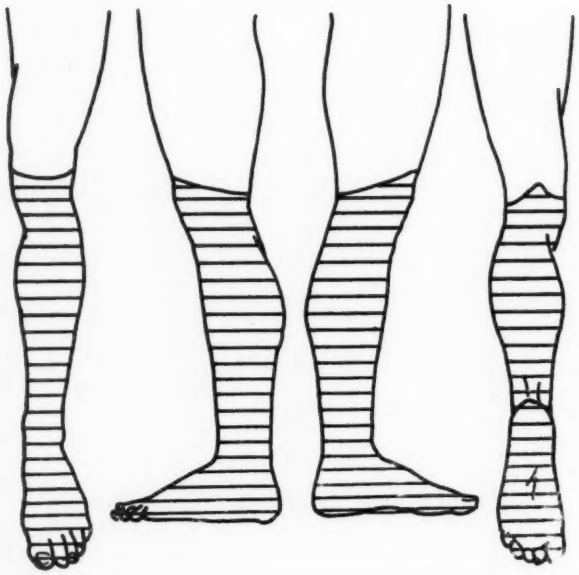

FIG. 3.—Area of gross impairment of sensibility to pin-prick in Case 3.

I examined him on November 10, 1950. He was quite well, working as a lift attendant, and had had no fits. The visual fields and cranial nerves were normal and there was no vestige of reflex, motor, or sensory abnormality in the upper limbs. In the legs there was bilateral increase of reflexes more marked on the left with increased tone in the left leg only. The right plantar was flexor, the left extensor. Power at the left knee was 80% normal, plantar flexion of the foot 60%, but in the dorsiflexors there was only a flicker of movement. Sensory findings were :—

	Right Leg	Left Leg
Position and Passive Movement		
Toes	5° correct	90° movement only
Ankle	5° correct	45° movement only
Knee	5° correct	10° direction correct
Vibration		
Ankle	7 secs. longer	Felt slightly
2-point		
Foot	No threshold	No threshold
Touch (wool)	9/10 9/10	4/10 5/10 4/10
Pin-prick	Normal	Gross impairment (see Fig. 3)
Temperature		
19°–42° : 32°–37°C Resolved		Resolved slowly
20°, 26°C Colder on right		
32°, 37°C Warmer on right		
These differences extended over the same area on the left thigh as did the hypoalgesia.		
Deep Pain		
0·2 ml. of 6% sodium chloride was injected into identical points in muscles of both legs. Very slight pain was felt on left but normal severe pain on right.		

Case No. 4 (*No.* 9616).—This man was wounded in the left parietal region on August 16, 1944, by mortar fragments. He was unconscious only a few minutes but had weakness of the right arm and leg. He was operated on by Lieut. A. E. James 18 hours after the injury. There was a fracture in the left parietal region. A burr-hole was made and enlarged to remove loose bone fragments. The dura was torn and the brain bruised and lacerated. Bone chips, a foreign body, and pulped brain were removed but there was no deep track. Twelve hours after operation he was able to move his right foot. He continued to make an uneventful recovery. He was examined in January, 1945, when there was found to be about 50% power in the right arm with slight spasticity and increased reflexes. Power in the right leg was 80% of normal. Position sense was lost in the right hand and impaired in the right foot, and, though touch appeared normal, there was hypoalgesia in the right arm and leg.

I examined him in November, 1950. Power in the right arm was about 60% for gross movements, but fine

finger movements were poorly performed. The right leg showed very little weakness but the foot was slightly spastic. Reflexes were slightly increased on the right side. Visual fields and cranial nerves were normal. He had no fits and was working well as a bank clerk.

Sensory findings were :—

Right Arm	Left Arm
Position and Passive Movement Fingers 30° movement only Wrist 20° movement only Elbow 10° direction correct	 5° correct 5° correct 5° correct
Vibration Much diminished	12 secs. longer
2-point No threshold	0·5 cm. correct
Touch (No. 1 nylon) 10/10 slightly diminished subjectively	10/10
Pin-prick Gross impairment up to upper arm	Normal
Temperature 15°–29° : 25°–45° : 30°–36°C Resolved both sides 15°, 25°, 29°, 30°, 36°, 45°C Felt same both arms	
Deep Pain 0·2 ml. of 6% sodium chloride was injected into identical sites in both arms. Severe pain experienced on the left, very slight ache on right.	

Right Leg	Left Leg
Position and Passive Movement Toes 20° direction correct	5° correct
Vibration Diminished	6 secs. longer
Touch (wool) 8/10 8/10	10/10
Pin-prick Gross impairment up to mid thigh	Normal
Temperature and Deep Pain As for arm	

Case No. 5 (*No.* 9639).—This man was wounded on August 19, 1944, by a fragment of a shell. He was never unconscious, and immediately noticed numbness and weakness of the left arm and numbness of the left face and tongue. He was examined at No. 6 M.N.S.U. within 12 hours of injury by Capt. P. L. M. Hartley, who found slight weakness of the left face. The left hand was profoundly weak, the arm less so, and it was noted that there was analgesia of the left hand. He was operated upon on August 21, 1944, by Capt. G. B. Northcroft. There was a parietal wound. The dural defect measured 1·5 cm. × 1·0 cm., and a track 2·5 cm. in length led down, from which bone fragments were removed. His recovery was uneventful (Fig. 4). He was examined again in February, 1946, by Dr. M. J. McArdle. There was still impairment of position sense and 2-point discrimination. There was analgesia

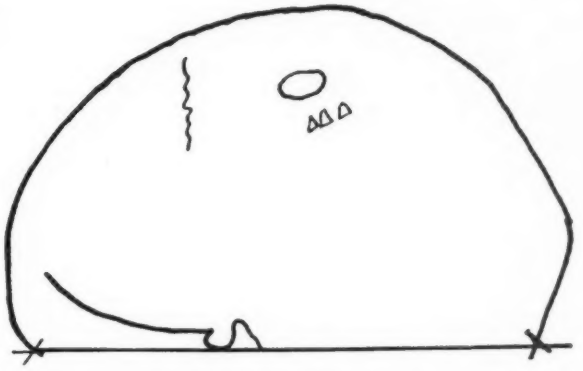

FIG. 4.—Tracing of lateral radiograph of skull showing site of wound in Case 5.

along the radial border of the left forearm with general hypoalgesia of the limb.

I examined him in September, 1950. He was well, working, and free from fits. The visual fields were full and the cranial nerves were normal. Power in the left arm was 80% of normal, except in the hand where there was only 20% power. The reflexes in the left arm were increased. Motor, sensory, and reflex findings in the legs were all normal. Sensory findings were :—

Right Arm	Left Arm
Position and Passive Movement Fingers 5° direction correct Wrist 5° direction correct	 20° movement only 10° direction correct
Vibration 4 secs. longer	Feels less
2-point 0·4 cm.	No threshold at 4 cm.
Touch (No. 2 nylon) 9/10 Wool 10/10 Finger dab 10/10	0/10 3/10 2/10 8/10 8/10
Pin-prick Normal	Gross impairment with loss along radial border (Fig. 5)
Temperature 16°–40° : 35°–39°C Resolved 16°, 35°, 39°, 40°C Same both sides	Resolved
Deep Pain 0·2 ml. of 6% sodium chloride injected into identical sites in both arms with resulting severe pain on the right, but very slight vague aching on the left.	

Case No. 6 (*No.* 11046).—This man was injured on February 27, 1945, when a shell fell near him. He recovered consciousness two minutes later and could see and hear normally, but both legs were numb and powerless. The left leg recovered in ten minutes but the right leg remained the same. He was seen at No. 1 M.N.S.U. some four hours later when paresis and loss of sensation in the right foot were noted. Major W. S. Keith operated next morning. There was

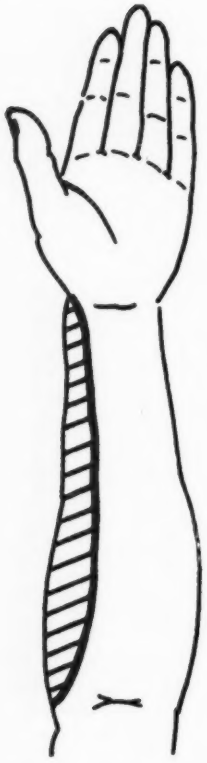

FIG. 5.—Area of loss of sensibility to pin-prick in Case 5.

a tiny penetration in the left frontal region with a small dural tear underlying. A superficial track ran backwards and on radiography a small foreign body was seen to lie superficially in the parietal lobe. He was examined by Dr. G. E. Smyth on March 19, 1945. There was a trace of right facial weakness, and in the right arm power was 90% normal with slight increase in the reflexes. In the right leg there was 90% power but tone and reflexes were increased, though the plantar response was flexor. On the sensory side position and vibration were impaired in the left foot; there was hypoalgesia of the foot but temperature was slowly but accurately resolved.

I examined the man five years later on August 25, 1950. The visual fields, cranial nerves, and arms were all normal. Power at the right knee was normal but was reduced to 60% in the right foot. The right knee and ankle jerks were increased but the plantar response was flexor. He had no fits. Sensory findings were :—

	Right Leg	Left Leg
Position and Passive Movement		
Toes	15° movement only 30° direction correct	5° correct
Vibration	Diminished	Normal
2-point	No threshold	0·4 cm.
Touch	Foot	
Wool	2/10 3/10	10/10
Finger dab	10/10	10/10
Pin-prick	Gross impairment	Normal
Temperature		
21°–41° : 28°–38°C	Resolved in 5 secs.	Resolved in 1 sec.
32°–37°C	Resolved in 5 secs.	Resolved in 1 sec.
28°C	Slightly colder on left	
32°, 37°C	Slightly warmer on left	
Deep Pain		
Not tested because facilities for sterile injection were not available where this patient was tested.		

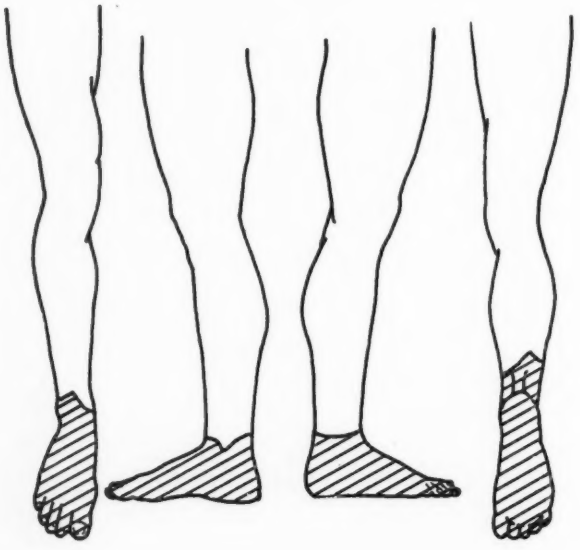

FIG. 6.—Area of gross impairment of sensibility to pin-prick in Case 6.

Case No. 7. (*No.* 9713).—This man was wounded on August 18, 1944, receiving bullet wounds over the vertex of the skull and in the right axilla. The right arm had to be amputated some three days later because of gas gangrene. He did not lose consciousness at the time of wounding, but immediately became aware of loss of power in both legs. He was seen at No. 8 General Hospital on the following day, by which time the right leg had largely recovered. The left leg was very weak but reflexes were not increased. Both plantars were extensor. Position sense was lost in the left leg. The visual fields were full. He was operated on by Major J. M. Small on August 20. Bone fragments and lacerated brain were removed from a cherry-sized cavity near the vertex to the right of the sagittal sinus (Fig. 7). On

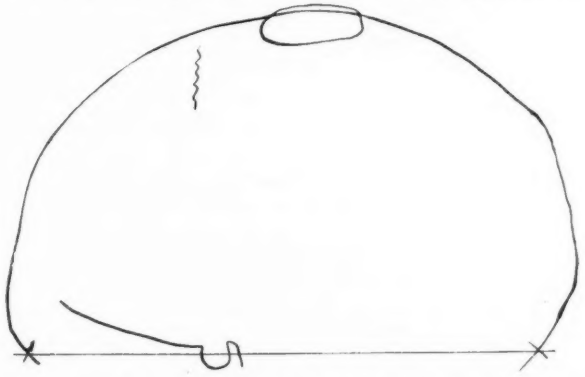

FIG. 7.—Tracing of lateral radiograph of skull showing site of wound in Case 7.

arrival at St. Hugh's Hospital, Oxford, on August 27, 1944, the left leg was still very weak but flaccid, the plantar response was extensor and joint sense was grossly impaired. Pin-prick was reported as normal.

He was examined by Dr. W. Ritchie Russell in February, 1945, when there was marked impairment of position and vibration sense in the left leg with very slight impairment of light touch. Threshold to pin-prick was raised but, when felt, the prick was associated with slight tingling.

I examined him on October 18, 1950. He had no fits and was happy at work as a time-keeper. The visual fields and cranial nerves were normal, as was the left arm and right leg. (The right arm had been amputated.) The left knee and ankle showed 60% power with slight increase in tone and reflexes and an extensor plantar response. Sensory findings were :—

Right Leg	Left Leg
Position and Passive Movement Toes 5° correct	5° movement only 30° direction correct
Vibration 9 secs. longer	Diminished
2-*point* Foot 4 cm.	No threshold
Touch (No. 1 nylon) 10/10	10/10
Pin-prick Normal	Gross impairment to mid-thigh
Temperature 20°–40° : 32°–38°C Resolved	Resolved
20°, 32°, 38°, 40°C Same both sides	
Deep Pain Not tested as facilities for sterile injection were not available where this patient was seen.	

Case No. 8 (*No.* 11795).—This man sustained a depressed fracture in the left parietal region at Arnhem on September 24, 1944. He was unconscious only a few minutes. Records of his subsequent progress are scanty as he was taken prisoner, but he had considerable dysphasia. The fracture was elevated on November 21. In February, 1945, he started with motor Jacksonian attacks involving the right hand but these ceased in 1948. He still has attacks in which he gets alternate freezing and burning sensations in the right index, middle, and ring fingers which rapidly spread up the arm and involve the right second and third divisions of the trigeminal nerve. The episodes last about a minute but there is no loss of consciousness. He was free from these episodes when examined.

I examined him in June, 1950. There was no field defect, and the cranial nerves, reflexes, and motor side were all normal. Sensory findings were :—

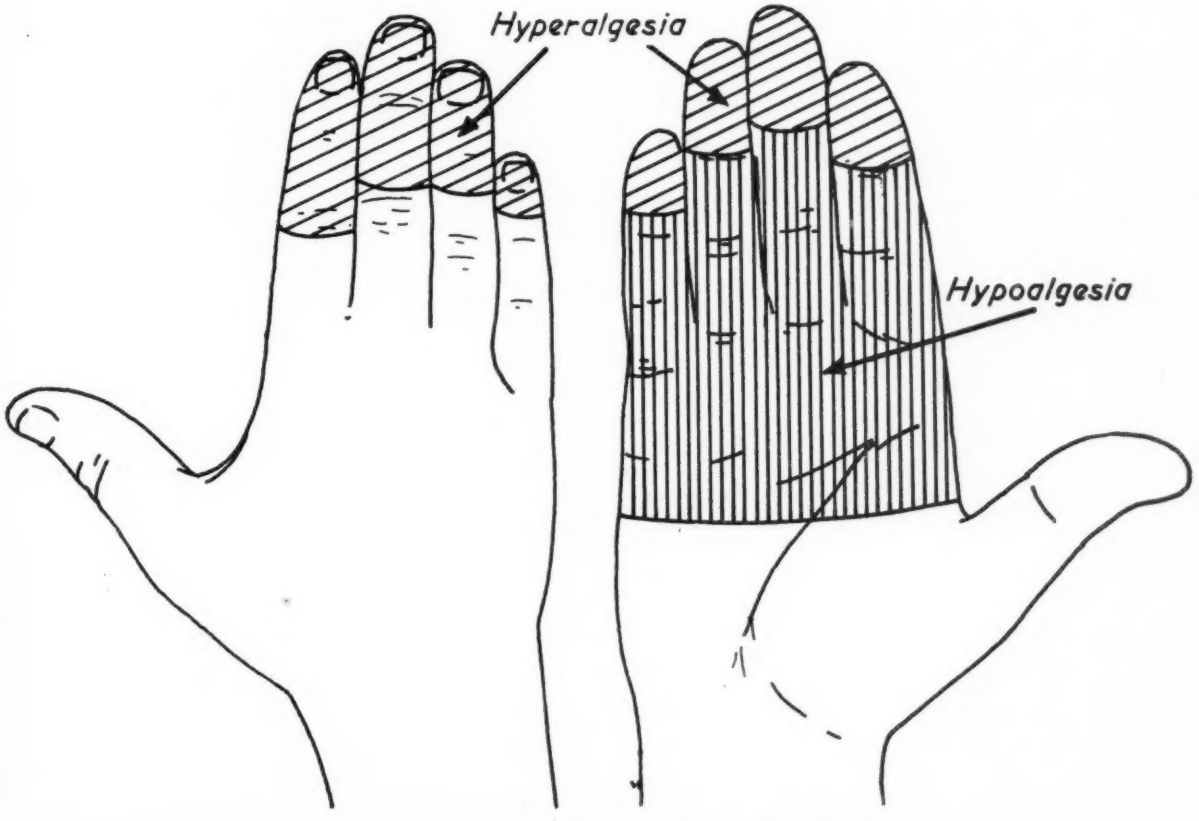

FIG. 8.—Areas of disturbance of sensibility to pin-prick in Case 8.

Right Arm	Left Arm
Position and Passive Movement Fingers 20° correct	5° correct
Vibration Diminished	8 secs. longer
2-point Fingers 0·4 cm.	0·4 cm.
Touch Fingers No. 2 nylon 5/10 6/10	10/10
Pin-prick See Fig. 8	Normal
Deep Pain 0·2 ml. of 6% sodium chloride injected into identical sites in small muscles of both hands with very slight pain on the right and severe pain on the left.	
Temperature 30°–36° : 34°–38°C Not resolved 43°, 41°, 39°C Hotter and painful on right 37°C Hotter on right thumb, index and middle fingers only 34°C Same both sides	Resolved
Sensory findings in the legs were all normal.	

Case No. 9. (*No.* 8800).—This man was wounded by a shell splinter in the right parietal region on June 26, 1944. He was unconscious for not more than two minutes. He was examined the same day by Capt. P. L. M. Hartley at No. 6 M.N.S.U. The visual fields, cranial nerves, and legs were normal but there was a flaccid monoplegia of the left arm with loss of all forms of sensation. He was operated upon by Major J. M. Small 36 hours after injury. The skull was fractured, and the dura was torn with indriven fragments of bone and metal. These were removed but the depth of the track was not stated. He was last examined jointly by Dr. W. Ritchie Russell and Dr. M. J. McArdle in November, 1945. He was then found to have severe impairment of position sense, 2-point, and touch in the left arm. In addition there was a gross raising of the threshold to pin-prick in the left hand.

I examined him in August, 1950. He was on full-time work and had no fits. The visual fields were full but there was a trace of left facial weakness. There was increase of tone and reflexes in the left arm, with power at 60% of normal. The legs were normal. Sensory findings were :—

Right Arm	Left Arm
Position and Passive Movement Fingers 5° correct Wrist 5° correct Elbow 10° correct	30° movement only 20° direction correct 10° direction correct
Vibration 9 secs. longer	Diminished
2-point 0·3 cm.	No threshold at 6 cm.
Touch Wool 10/10 Finger dab 10/10	1/10 7/10
Pin-prick Normal	Gross impairment with 1 sec. delay up to wrist
Temperature 23°–41° : 30°–35°C Resolved 34°–39° : 39°–43°C Resolved 23°, 30°, 35°, 41°C Normal	Resolved Not resolved Delay of 4 secs.

Right Leg	Left Leg
Position and Passive Movement Toes 5° correct	5° correct
Vibration Normal	Normal
Touch No. 1 nylon 6/10 5/10 Wool 10/10	8/10 7/10 10/10
2-point 2·5 cm.	No threshold at 7 cm.
Pin-prick Normal	Feels same but delay of 1 sec.

Case No. 10.—This man was wounded in 1916 in the left parietal region.

The period of post-traumatic amnesia is uncertain but was probably less than 48 hours. He was left with weakness of the right hand and some difficulty in writing. His speech was unaffected. Initially he had some fits but he had been free for ten years.

I examined him in December, 1950. There was no verbal dysphasia but there was some dysgraphia. The visual fields were full and cranial nerves were normal. Power in the right hand was 80% normal and the reflexes were slightly increased. The legs were normal.

Sensory findings were :—

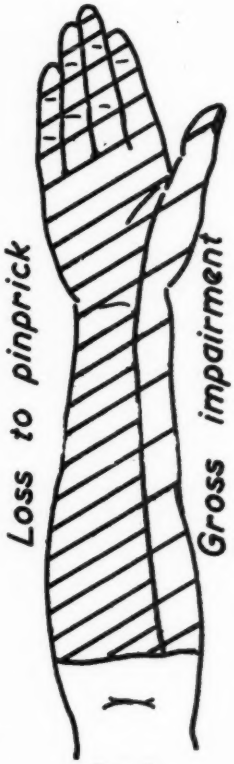

FIG. 9.—Areas of impairment of sensibility to pin-prick in Case 10.

FIG. 9

Right Arm		Left Arm
Position and Passive Movement		
Fingers	90° failed	5° correct
Wrist	20° movement only	5° correct
Elbow	10° direction correct	5° correct
Vibration		
Wrist	Lost	Normal
Elbow	Diminished	Normal
2-point	No threshold at 5 cm.	0·4 cm.
Touch		
No. 2. nylon	0/10 in forearm	10/10
Wool	0/10 in forearm	10/10
Pin-prick	See Fig. 9	Normal
Temperature		
28°–42° : 15°–48°C Not resolved		Resolved
Deep Pain		
0·2 ml. of 6% sodium chloride injected into right hand with no pain.		

Case No. 11. (*No.* 10910).—This patient sustained a penetrating wound of the right parietal region in February, 1945. He did not lose consciousness. He was

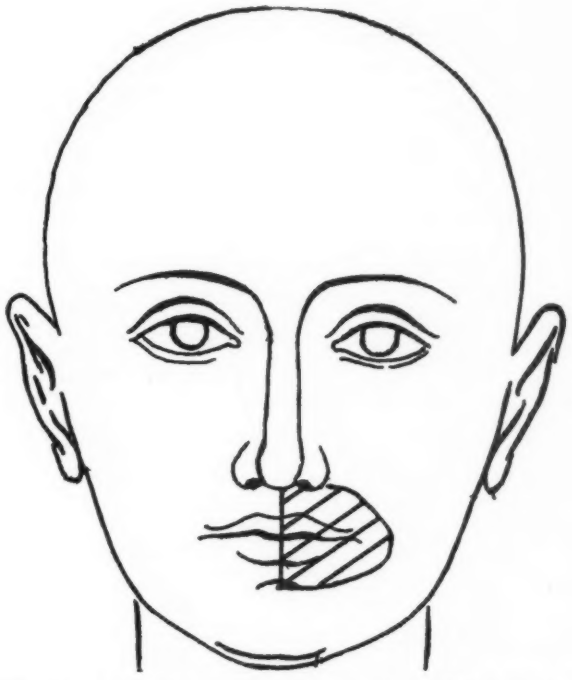

FIG. 10.—Area of gross impairment of sensibility to pin-prick on face in Case 11.

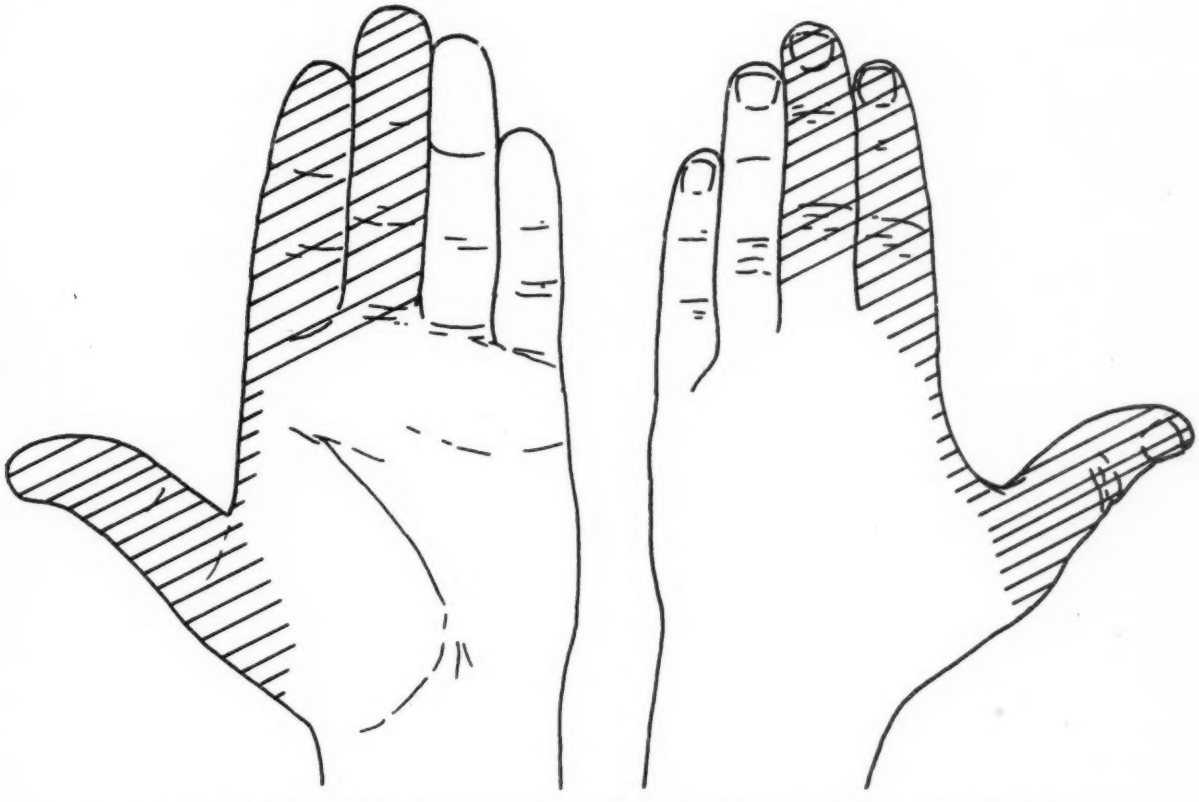

FIG. 11.—Area of gross impairment of sensibility to pin-prick in left hand in Case 11.

examined at No. 1. M.N.S.U. eight hours later by Major C. C. Grey when he was found to have weakness of the left face and hand with impairment of position sense, 2-point, touch, and pin-prick in the left hand also. He was operated upon 26 hours after injury by Major W. S. Keith. A ¾ in. tear in the dura was found and a small amount of necrotic brain lay below. He was finally examined in April, 1945, by Dr. G. E. Smyth when there was a trace of left facial weakness and an area of hypoalgesia over the left upper and lower lip and some impairment of pain sensation in the left hand.

I examined him in February, 1951. He was at work as a storekeeper and had no fits. There were no motor disturbances and the visual fields were full. The cranial nerves were normal except for the trigeminal in which territory there was hypoalgesia. The sensory findings were as follows :—

Right Arm	Left Arm
Position and Passive Movement Fingers 5° correct	5° correct
Vibration 7 secs. longer	Diminished
2-point 0·5 cm.	0·5 cm.
Touch (No. 2 nylon) 10/10	10/10
Pin-prick Normal	See Figs. 10 and 11
Temperature 32°–36° : 36°–40°C Resolved 32°, 36°, 40°C Same both sides	Resolved
Deep Pain Not tested.	

Series B.—This group consisted of patients with cortical wounds with hyperpathia.

Case No. 12. (*No.* 11635).—This patient sustained a through and through wound from a rifle bullet, from the right parietal to the left occipital region, on April 20, 1945. He had post-traumatic amnesia lasting for 15 minutes. He was examined at No. 6 M.N.S.U. by Capt. A. C. Watt the next day. He appeared to have light perception only. There was a slight weakness of the left face with marked paralysis of the left arm. The leg was only slightly weak. Reflexes and tone were increased on the left but the plantar response was flexor. All modalities of sensation appeared to be depressed on the left. Operation was performed the same day. Both wounds were small as were the tracks joining them. These were sucked clear of clot and after irrigation with penicillin were closed. Two days later further clot had to be removed from the right parietal wound. He was last examined in December, 1945, when impaired sensation on the left side was noted.

I examined him on August 8, 1950. The visual fields were full, but there was defective localization in the left homonymous field. Power in the left shoulder and elbow was 80%, but in the hand there was only slight movement. Power in the left leg was about 60%. There was increase of tone and reflexes on the left side and the left plantar response was extensor. He had no fits. Sensory findings were :—

Right Arm	Left Arm
Position and Passive Movement Fingers 5° correct Wrist 5° correct Elbow 5° correct	 50° movement only 10° movement only 10° direction correct
Vibration 8 secs. longer	Diminished
2-point 0·4 cm.	No threshold
Touch Fingers Wool 10/10 No. 2 nylon 8/10 7/10 Arms Wool 10/10	 8/10 7/10 8/10 10/10
Pin-prick Normal on right ; on left pain is much more severe, spreads over an area, and lasts longer ; likewise on trunk and second and third divisions of trigeminal.	
Temperature 23°–39° : 34°–38°C Resolved 39°, 38°C Warmer on right 37°C Same both sides 36°, 34°, 23°C Colder on right	Resolved

Right Leg	Left Leg
Position and Passive Movement Toes 5° correct Ankle 5° correct Knee 5° correct Hip 5° correct	 Lost 45° movement only 20° movement only 10° direction correct
Vibration 3 secs. longer	Diminished
Touch Foot Wool 10/10 No. 2 nylon 10/10	 9/10 5/10
Pin-prick As for arm	

The left half of the scrotum was not hyperalgesic to pin-prick, nor was the ophthalmic division of the trigeminal nerve on the left.

Case No. 13. (*No.* 18403).—This man sustained a wound in the left parietal region in July, 1944, by a bullet from a Sten gun. He was unconscious for less than five minutes and on recovery found weakness and numbness of the right arm and leg and some difficulty with his speech. There was no visual defect. The speech and leg recovered rapidly but he had persistent weakness and sensory disturbance in the right arm. In December, 1944, he developed grand mal epileptic attacks with a frequency of one every six months.

I examined him in September, 1950. He was at work regularly as an electrical welder. His last fit was in June, 1950, on the occasion of a dental extraction, and before that he had been free from fits for 18 months. He had a momentary loss of consciousness a month before examination. The visual fields and cranial nerves were

normal, as also were the legs. The right arm showed 80% normal power, the hand 60%, and the arm reflexes were increased.

Sensory findings were :—

Right Arm	Left Arm
Position and Passive Movement	
Thumb and index 5° correct	5° correct
3 4 5 digits 30° direction correct	5° correct
Vibration Normal	Normal
2-point	
Thumb and index 0·5 cm.	0·5 cm.
3 4 5 digits No threshold at 4 cm.	0·5 cm.
Touch (No. 2 nylon)	
Thumb and index 10/10	10/10
3 4 5 digits 2/10 1/10	10/10
Pin-prick	
Thumb and index normal	Normal
3 4 5 digits Much more painful than right thumb and index or than left hand	Normal
Temperature	
20°–36° : 28°–35°C Resolved	Resolved
20°C Colder on right 3 4 5 digits than on left	
28°, 35°C Same both sides	

Series C.—This comprised patients with cortical wounds with impairment of temperature sense but in whom the sense of pain was preserved.

Case No. 14. (*No.* 8715).—This man was wounded on June 20, 1944, by shell splinters. He was thrown on the floor by the force of the explosion but did not lose consciousness. He was examined at St. Hugh's Hospital, Oxford, on June 22, 1944, by Dr. M. J. McArdle. He was somewhat drowsy, but was quite rational and well orientated. There was an attention defect in the left half visual field and a left facial weakness. The left arm showed moderate decrease in power with depressed reflexes ; the left leg was only slightly weak. Both plantars were extensor. On the sensory side there was noted to be postural impairment in the left fingers and toes. He was operated upon on June 23. There were three wounds in the right parietal region, two of which were superficial. Below the third wound was a small depressed fracture which was included in a burr-hole. Beneath this was a dural tear measuring 0·3 cm. × 0·2 cm., from which led a small track 1 cm. in depth, where a bone chip was lodged. This was removed. The last recorded examination was made by Dr. M. J. McArdle on July 3, 1944. He found severe disturbance of position and vibration sense in the left arm with slighter affection of the leg. Light touch and temperature sense were likewise severely diminished in the left arm. Superficial pain and pressure pain were, however, on several testings found to be unaffected.

I examined this man six years later, on October 17, 1950. He had kept well, was free from symptoms, hard at work as a farmer, and had had no fits since his discharge from hospital, where he had two Jacksonian attacks involving the left face and arm. General power in the left arm was good, apart from finger flexion which was still only 40%. Reflexes were equal, plantars flexor, visual fields were full and the cranial nerves intact. The legs were normal.

Sensory findings were :—

Right Arm	Left Arm
Position and Passive Movement	
Fingers 10° correct	10° correct
Vibration Normal	Diminished
2-point 0·5 cm.	No threshold at 4 cm.
Touch Wool 10/10	4/10 5/10
Finger dab 10/10	10/10
Pin-prick Normal	Normal
Temperature	
20°–43°C Resolved	Not resolved
43°C After long delay felt slightly warm	
Deep Pain	
0·2 ml. of 6% sodium chloride was injected into identical sites in the muscles of both arms with production of exactly the same degree of pain.	

Case No. 15. (*No.* 9469).—This man sustained a mortar wound of the right posterior parietal region in August, 1944. His post-traumatic amnesia did not develop until half an hour after injury during which time he noted that his left arm and leg felt numb. The amnesia lasted from 12 to 24 hours. He was operated upon by Col. C. A. Calvert some 48 hours later. There was a small dural tear with a track 4 cm. deep. In March, 1945, he had a fit beginning in the left arm, since when he had eight or nine in all, the last in June, 1950.

I examined him in August, 1950. He was at work as a manager of a building firm. The visual fields and cranial nerves were normal. There was no motor weakness, but reflexes in the left leg were slightly increased. Plantar responses were flexor.

Sensory findings were :—

Right Arm	Left Arm
Position and Passive Movement	
Fingers 5° correct	5° correct
Vibration Normal	Normal
Touch (No. 2 nylon) Normal	Normal
2-point 0·3 cm.	0·3 cm.
Pin-prick Normal	Normal

Right Leg	Left Leg
Position and Passive Movement	
Toes 5° correct	5° movement only
Ankle 5° correct	10° direction correct
Vibration 3 secs. longer	No subjective impairment
2-point 2 cm.	2 cm.
Touch	
No. 1 nylon 6/10	5/10
No. 2 nylon 10/10	10/10
Pin-prick Normal	Normal
Temperature	
23°–43°, 23°–36°, 25°–31°, 39°–44°C Resolved both legs	
23°, 31°C Feels colder on the left	
35°C Feels same both sides	
39°, 43°C Feels warmer on the left	
Appreciation of temperature takes 2 secs. longer on left.	
Deep Pain	
Not tested owing to lack of facilities for sterile injection where this patient was examined.	

Series D.—This consisted of patients with extensive wounds with loss of discriminative sensibility, but in whom the sense of pain was preserved.

Case No. 16. (*No.* 8911).—This officer was wounded in the right parietal region on June 10, 1944, by a shell splinter. He was unconscious for three days. He was examined by Capt. R. Jepson on June 11, when there was found a left homonymous hemianopia and a left hemiplegia with an extensor plantar response. Capt. R. Jepson operated the same day. There was a dural defect measuring 1 in. × ½ in. and a moderate-sized cavity with indriven bone fragments. He was finally examined in September, 1945. He had a defect in the left upper quadrant of the visual fields and a mild left hemiplegia. Position sense was impaired on the left side but pin-prick was normal.

I examined him in August, 1950. There was no demonstrable field defect and the legs were normal. There was a fair degree of weakness in the left arm. He had no fits. Sensory findings were :—

Right Arm	Left Arm
Position and Passive Movement	
Fingers 5° correct	90° movement only
Wrist 10° correct	20° direction correct
Vibration Normal	Slight subjective diminution
2-point 0·3 cm.	No threshold
Touch (No. 2 nylon) 10/10	10/10
Pin-prick Normal	Normal
Temperature	
36°–40°C Resolved	Resolved

Right Leg	Left Leg
Position and Passive Movement	
Toes 5° correct	30° correct
Vibration Normal	Normal
2-point 2·5 cm.	7·5 cm.
Touch	
No. 2 nylon 10/10	9/10
Wool 10/10	10/10
Pin-prick Normal	Normal
Deep Pain Not tested	

Case No. 17. (*No.* 12249).—This patient sustained a through and through wound with entry in the left occipital region near the midline and exit in the parietal region near the midline on the same side on April 20, 1945. He was unconscious for a few minutes only. He was examined the following day at No. 4 M.N.S.U. when he was found to have a right hemiparesis with weakness and increased tone in the left leg also. Position sense was lost on the right. He was operated upon the same day when there was a gutter 5 cm. in depth between entry and exit wounds.

I examined him in March, 1950. The visual fields were full, but he had a fairly dense hemiplegia on the right side. The right plantar was extensor, the left flexor. He had two fits in 1945 but none since. Sensory findings were :—

Right Arm	Left Arm
Position and Passive Movement	
Fingers 90° failed	5° correct
Vibration Diminished	Normal
Touch (wool) 10/10	10/10
Pin-prick Normal	Normal

Right Leg	Left Leg
Position and Passive Movement	
Toes 90° failed	5° correct
Vibration Diminished	Normal
Touch (wool) 10/10	10/10
Pin-prick Normal	Normal
Deep Pain	
0·2 ml. of 6% sodium chloride injected into identical sites in arms and legs. There was no difference in the degree of pain experienced.	

Case No. 18: *Cortical Neoplasm with Pain Loss.*—A married woman of 43 years was admitted to the Manchester Royal Infirmary, under the care of Dr. Fergus R. Ferguson, on January 21, 1946. Her history was that six months previously she had begun with right-sided Jacksonian attacks with unconsciousness lasting up to 20 minutes. In all she had had five of these attacks. On December 12, she began to lose the power in her right arm and leg, and she also developed difficulty in speaking.

On admission she was markedly dysphasic. Her mental condition was, however, excellent, as was shown by her agitation when her husband made errors in giving her history for her and the signs she made in order to correct him. Examination showed a spastic weakness of the right arm and leg with involvement of the right face. The visual fields and cranial nerves were otherwise normal. On the sensory side there was marked astereognosis and loss of position sense. There was a marked hypoalgesia to pin-prick over the whole of the right side extending to within 1 or 2 cm. of the midline. On February 2, 1946, she had a further fit, following which she rapidly passed into coma and died. At necropsy there was found in the left fronto-parietal region a tumour 6 cm. in diameter which proved to be an isomorphic glioblastoma. The growth was mainly cortical and the thalamus was definitely not invaded.

Discussion

The first concern in presenting material of this kind must be to anticipate a series of objections which, if sustained, might render any succeeding deductions invalid. The cases in this report have been chosen especially with a view to avoiding these pitfalls. Thus, unlike neoplasms, traumatic material gives little uncertainty as to the extent of the lesion, for in two-thirds of these cases the depth of the wound at the end of an operation is given. Of the remainder, Case 8 has only a scanty operative report, but as he had only a depressed fracture the underlying injury can only have been superficial. In Cases 9 and 10, notes about the depth of the wound are also lacking, but as the resultant deficit was monoplegic in distribution the wound cannot have been deep. Of the remaining cases no wound was deeper than 3 cm. except in Case 15 where the track was 4 cm.

Further evidence as to the superficial nature of the wound is obtained from a consideration of the resultant neurological deficit. Thus in Series A the residual deficit was monoplegic in distribution in nine instances, while in the two other cases (Cases 2 and 4) both arm and leg were involved.

It is worth noting that in Cases 8, 9, and 10, where the operative details are scanty, the neurological deficit was only monoplegic in distribution. There can, therefore, be no hesitation in affirming that these wounds did not involve the thalamus but were cortical in site and effect.

The second fallacy which must be considered is the occurrence of oedema, pressure, and vascular disturbances around the site of the lesion. Russell (1945) has pointed out that there are frequently marked sensory changes in brain wounds which recover rapidly as the effects of shock pass off. In the present series there can be no possibility of the findings described being transient, as the shortest period elapsing between wounding and the last examination was two years. Moreover, the findings in the final examination were substantially the same as the last previously recorded examination, indicating that the condition had achieved stability.

The possibility of remote cerebral damage due to concussion has been avoided by omitting cases with a long post-traumatic amnesia. Thus in Series A, B, and C, 12 cases were unconscious less than five minutes, one less than 15 minutes, and the remaining two less than 48 hours.

A further source of error stressed by Holmes (1927b) is the altered sensory findings which may follow epileptic attacks. In the present series nine of the 15 cases had never had a fit. Of the remainder, Case 10 had been free for ten years, Case 14 for six, and Case 8 for two years, except for momentary sensory disturbance without loss of consciousness. Cases 2 and 13 had no attacks in the three months before examination and Case 15 had been free for two months. The sensory findings were not, therefore, due to epileptic disturbances. Also the sensory findings were constant and unvarying, a feature most unlike a post-ictal phenomenon.

The possibility that the areas of sensory loss are hysterical might be raised, but great care has been taken that no such suspicion could be directed against the cases in the present series. The personality of all the patients was good, and at no stage had they shown any evidence of psychiatric disturbance. Since discharge from hospital they had good work records. Their attitude to examination was cooperative and critical. Further objective evidence as to the absence of hysteria from these cases is seen in the occurrence of dissociated sensory loss. For example, in Case 2, though pin-prick was impaired on the left side, temperature sense was normal in the arm and delayed though accurate in the leg. In Cases 3 and 5 sensory charts made without any prompting or suggestion were exact replicas of charts made five and four years previously. Case 9 had a raised threshold to pin-prick, confined to the left hand in 1945, a finding confirmed in 1950. Case 10 was analgesic over the right fingers and palm but only hypoalgesic over the thumb. Moreover, these sensory observations have been repeatedly confirmed in the present

study, and every effort was made to shake the patient's constancy in asserting that he could not feel pain or pin-prick in an area. There can, therefore, be no doubt that the sensory findings recorded here were not hysterical in origin.

A final difficulty to be avoided is that referred to by Head (1920) when he wrote :

> " A second difficulty arises from the fact that the first effect produced by pricking with a sharp needle is recognition of an acutely pointed object ; further pressure adds to this a sensation of pain. It is almost impossible to prevent the patient saying he is pricked, whenever he appreciates that the stimulus is a sharp point, and, if he is told to wait until he obtains a distinct sensation of pain we run the risk of placing the threshold too high."

From this Head argued that in cases of so-called hypoalgesia from cortical lesions it was the " sense of point," a discriminative faculty, that was lost and not pain sense. Though these two elements may be concerned in any pin-prick it is easy to ascertain from testing colleagues that it does not require a very heavy thrust to ensure that both the " sense of point " and painful elements are called into action. In the present series of tests care has always been taken in confirming an area of pain loss to thrust very heavily. Comparable thrusts on the opposite side raised strenuous objection from the patients.

A further test for pain which has also been employed is entirely free from such objections. Kellgren (1938a and 1938b) in his studies on deep pain found that the injection of hypertonic sodium chloride was a convenient method of producing pain in deep structures. The injection into muscles of 0·2 ml. of 6% sodium chloride has been used in these studies. Once the needle is removed there is no complicating factor and a pure pain stimulus is produced. The pain is quite severe, and there is no possibility of doubt or confusion in comparing a normal and a hypoalgesic area. It is contended, therefore, that in this series we have cases of cortical damage which are free from the objections discussed above.

In examining the records of so large a series of penetrating wounds a remarkable feature is the striking, dissociated sensory losses which have been observed. Not infrequently position sense would be entirely normal but severe impairment of 2-point discrimination would occur and vice versa. These findings appear surprising to those more accustomed to observing the sensory changes wrought by the progress of natural disease, for here discrete, permanent, dissociated sensory deficits are the exception rather than the rule.

These features are illustrated in Series C where two examples of dissociation between pain and temperature sense are presented. In Case 14 deep and superficial pain were quite normal, whilst temperature appreciation was almost lost, and in Case 15 there was appreciable delay. These cases illustrate that not only can dissociation of discriminative sensibilities occur as a result of cortical wounds but also the so-called thalamic sensations such as pain, temperature, and touch can be separately affected. These illustrations have been included to provide further evidence of how specific in their effects these wounds can be.

Series B consists of two cases of cortical wounding in which there was hyperalgesia, extending in Case 12 over one half of the body and in Case 13 being segmental in distribution. Now though it may be suggestive, nevertheless it is not valid to argue that because a cortical lesion causes hyperalgesia, therefore the convolutions damaged must be the centre for the representation of pain. However, it is valid to suggest that whereas it was formerly considered that hyperalgesia was pathognomonic of a lesion confined to the thalamus, it appears that this so-called thalamic symptom of excessive response to painful stimuli may be produced by cortical lesions.

The Series A cases need no elaboration as far as the facts are concerned. The patients had pain impairment both superficial and deep and their lesions were cortical in site. Series D illustrates the anomaly mentioned by Russell (1945) that whereas extensive cortical injury can leave pain sensibility intact, a small cortical wound may impair pain sensation on the contralateral side. These cases conformed to the classical neurological description of the effects of cortical lesions. They had more extensive wounds, yet though position sense and 2-point discrimination were impaired, pain sensibility remained unaffected. It remains, therefore, to try to construct a hypothesis to explain these facts.

Le Gros Clark (1932) showed that degeneration of the thalamus follows ablation of the cortex, thereby stressing the importance of cortico-thalamic projections, which, as McCulloch (1944) has shown, are most dense from the posterior lip of the central fissure. Dusser de Barenne and McCulloch (1938), by their method of neuronography, showed that while strychninization of a small area of the thalamus produced spikes in a wider area of the sensory cortex, symptoms were only referred to that part of the body represented by the part of the thalamus initially stimulated. A feed-back was established from the cortex to the thalamus which raised the excitation of the already stimulated thalamic cells to a level sufficient to produce a sensation. Other thalamic areas, not being already

in a state of excitation as a result of afferent stimuli from the periphery, did not achieve a liminal degree of excitation as a result of feed-back from the wider stimulated cortical area. Thus we see established from both anatomical and physiological viewpoints the close mutual relationship between cortex and thalamus, a partnership on equal terms, rather than the former concept of cortical dominance.

As a result of these various contributions the idea of an impulse passing from the periphery to the thalamus and thence to the cortex from where a circuit back to the thalamus again becomes established, arose. It matters little for our present purpose whether with Bremer and Bonnet (1949) we think that the main circuits are intracortical and it is not until these have been built up that the thalamus is finally fired, or whether with Chang (1950) we consider that these reverberating circuits lie exclusively between cortex and thalamus. The essential fact is that the final elaboration of the sensory impulse depends on mutual activation of thalamus and cortex.

Now as Earl Walker (1949) has pointed out, the mode of establishment of these circuits is by mechanisms such as recruitment, facilitation, and summation common to neuron pools throughout the nervous system. The agents which transmit excitation or inhibition to a neuron are the *boutons terminaux* which are in contact with its surface. The resultant of the excitatory and inhibitory influences determines the activity of the cell. Liddell (1934) showed that in a spinal cord lesion the impulses delivered by many such *boutons* are cut off at their source and hence the receptor neuron, until it can readjust to the changed conditions of activity, ceases to function. This condition is spoken of as the period of spinal shock.

It is pertinent to note, as Russell (1945) has pointed out, that even following small cortical wounds with no disturbance of consciousness pain sensibility is often lost for several days but ultimately it recovers. He suggested that this was a shock effect of the type described by Liddell (1934). In the terms of the observations described above this " shock " effect can be conceived as affecting the cortico-thalamic circuits which are essential for the conveyance of sensation to consciousness. In many cases these circuits are able to readjust and re-establish themselves and pain sensibility recovers. In other cases, however, such as those presented in this study, the damage to these circuits at their cortical end is such as to preclude their re-establishment and hence pain loss becomes a permanency.

Why then, when wider areas of cortex are destroyed does pain often recover? As was pointed out above, stimulation of a group of thalamic cells fires a much wider area of cortex (Dusser de Barenne and McCulloch, 1938) but symptoms are only referred to that part of the body subserved by the part of the thalamus originally stimulated which has been fed-back from the reciprocal area of the cortex. The remaining cortico-thalamic circuits produce no effects. They do, however, constitute a net in which the impulse may expend itself, albeit fruitlessly, when it is blocked from its primary pathway. When, however, cortical damage, and hence thalamic degeneration, is widespread such pathways are no longer available and the impulses may then be passed to the contralateral cortico-thalamic circuits and pain is felt.

Why then do the discriminative aspects of sensibility not undergo similar re-adjustments? The reason is perhaps but an illustration of Hughlings Jackson's law that the higher and more specific aspects of any function are the first to be affected, the last to recover, and the least capable of effecting any re-adjustment. In physiological terms, as described by von Bonin (1950), the complexity of the nerve net required to subserve discriminative functions is so great as to make alternative pathways difficult. The more primitive sensations on the other hand have more simple nets and can more readily utilize alternative routes.

In conclusion, therefore, it may be asked, " Is pain represented in the cortex " ? If by representation we mean an end-station or a highest level as was meant by Head, it must be answered, " No ". If, however, we mean, " Is the cortex concerned in the appreciation of pain " ? it is submitted that the cases presented here show that the cortex is intimately concerned with appreciation of pain and the hypothesis is offered as an explanation in conformity with modern neurophysiological concepts.

Summary

The historical development of the current view with regard to the central representation of pain is described.

Eleven cases of cortical wounds with impairment of pain and temperature sense are described.

Two cases of cortical wounds with persistent hyperpathia are presented.

Two examples of small cortical wounds with impairment of temperature sense but preservation of pain sensibility are recorded.

Two cases of extensive wounds with loss of discriminative sensation but with pain sense preserved are described.

It is suggested that the cerebral cortex is concerned with pain sensibility; and a hypothesis to explain the paradox, that whilst small cortical

wounds may affect pain larger wounds often do not, is presented.

I wish to thank Dr. W. Ritchie Russell for his kindness in granting me access to the records of the Head Injury Advice Bureau and for permission to examine the patients; also to Miss Martin-Hurst, Almoner at the Bureau, without whose personal knowledge of and tactful approach to the patients, it would not have been possible to persuade so many of them to return for re-examination. I also wish to thank Dr. Fergus R. Ferguson for permission to quote Case 18.

In addition tribute must be paid to the many neurologists and neurosurgeons, without whose careful observations and meticulous records, made often under difficult conditions in the field, so fine a series of cases would not have been preserved, and this study would not have been possible.

Finally I wish to thank Brigadier W. R. D. Hamilton, O.B.E., Consultant Physician, the War Office, for permission to publish.

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CONFIRMATION OF THE ROSENOW ANTIBODY-ANTIGEN SKIN REACTION IN IDIOPATHIC EPILEPSY

BY

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Rosenow (1947b) has reported the isolation of an immunologically identifiable strain of alpha streptococcus from patients with idiopathic epilepsy. He also reports that the intradermal injection of antibodies specific for this strain elicits an erythematous skin reaction in patients harbouring this organism, and in a high percentage of other epileptic patients as well. This paper presents an investigation and a statistical verification of this reaction in epileptic patients in England ; antibodies prepared in the United States from organisms isolated there were used.

Materials and Methods

Two groups of patients were tested at the National Hospital ; one consisted of patients considered to have idiopathic epilepsy ; the other was made up of unselected patients from the out-patient clinic. The number and sex distribution of the test groups was similar, but the average and mode age of the epilepsy group was younger. It will be shown that this does not affect the results or conclusions. A comparison of the two groups is given in Table I.

TABLE I

COMPOSITION OF THE TEST GROUPS

	Control Group	Epilepsy Group
Total ..	105	117
Sex : Men ..	53	58
Women ..	52	59
Age spread ..	4–77 years	3½–72 years
mean ..	47·5 years	26·9 years
mode ..	4th–5th decade	2nd decade

Specific antibodies for strains of alpha streptococci isolated from the nasopharynx of patients with idiopathic epilepsy, multiple sclerosis, schizophrenia, arthritis, and migraine were made by Dr. E. C. Rosenow (1947a and b ; 1948b, c, and d) in Cincinnati, Ohio, U.S.A., and sent by air mail to England. He also prepared and sent a control test solution of 0·9% NcCl containing 0·02% phenol.† For purposes of discussion, the diseases of the patients from whom the alpha streptococci were isolated will be used to identify the test antibodies.

All patients were tested with all antibodies whenever possible. The volar surface of the forearm was found to be the most convenient area for the test, though other areas would serve as well. After the skin was washed lightly and allowed to dry, 0·03 ml. of the test material was injected intradermally, and the maximum flare which usually appeared within five minutes was outlined with ink or skin pencil. The area of erythema was measured in square centimetres by superimposing circles of known area drawn on cleared radiograph film. All tests were done by the same person, who, when this was possible, had no knowledge of the clinical diagnosis.

In considering the results, the difference between the reaction produced by the saline phenol control solution, and that produced by the test antibody has been used as the measure of reactivity to the antibody.

Results

The mean reaction of the epilepsy group to the " epilepsy " antibody was 9·42 cm.^{2} with a spread of 0·0 to 19·62 cm.^{2}, and a standard deviation of 4·72 cm.^{2} The mean control group reaction to this antibody was 1·87 cm.^{2} with a spread of 0·0 to 13·89 cm.^{2}, and a standard deviation of 2·09 cm.^{2} It at once appears that this is a true difference. Calculation shows that the probability of this being a chance variation is, for practical purposes, zero.

Comparison of the other means shows a significant difference between the mean reaction of the two groups to the " migraine " and " arthritis " anti-

* Moseley Travelling Fellow, Harvard Medical School, at the time this work was done.

† This concentration of phenol was used as a preservative in the antibody solutions.

TABLE II

COMPARISON OF THE ERYTHEMATOUS REACTION OF EPILEPTIC AND NON-EPILEPTIC PATIENTS TO ANTIBODIES ISOLATED FROM PATIENTS WITH VARIOUS DISEASES

Alpha Streptococcus Isolated from Patients with	No. Tested		Difference in Area (in cm.²) of Reaction between Test Antibodies and Saline-phenol control								Comparison of the Means	
			Mean		Spread		Standard Deviation from Mean		Standard Error of Mean			
	Control Group	Epileptic Group	Control Group	Epileptic Group	Control Group	Epileptic Group	Control Group	Epileptic Group	Control Group	Epileptic Group	Critical Ratio	Probability
Idiopathic epilepsy ..	105	117	1·87	9·42	0·–13·9	0·–19·6	2·09	4·72	·204	·442	15·56	≅ 0
Migraine	102	77	2·51	3·54	0·–12·6	0·–12·6	2·84	2·87	·289	·326	2·39	≅ ·02
Disseminated sclerosis	101	77	2·01	2·13	0·– 8·8	0·–12·5	1·75	2·38	·175	·270	0·26	≅ 0·8
Arthritis	101	80	1·68	2·50	0·– 7·9	0·– 8·0	1·66	2·63	·167	·293	2·43	≅ ·02
Schizophrenia ..	68	78	1·70	2·40	0·– 8·9	0·–10·7	1·82	2·29	·227	·261	2·02	≅ ·05

bodies, but these means are too close to be of importance in any one patient. These results are summarized in Table II.

In order to determine any effect the age difference of the two groups might have had, a study was made of those patients from the fourth and fifth decade, the mode of the control group. Thirty-one epileptic patients and 45 control patients fell into this age range. There were about half from each decade, and they were evenly split between the sexes. The mean epileptic group reaction to the epilepsy antibody was 8·14 cm.² with a standard deviation of 3·69 cm.², while the control group mean was only 1·43 cm.² with a standard deviation of 1·66 cm.² Comparison of the means gives a critical ratio of about 10, which indicates that the probability of such a chance variation is again zero for practical purposes. There were too few patients in the control group whose age was at the mode of the epileptic group to make a similar comparison at that age.

If a reaction greater than the mean reaction of the control plus two standard deviations is taken as significant (i.e. 6·05 cm.²), 78·8% of the patients with idiopathic epilepsy had positive reactions to the " epilepsy " antibody. This is somewhat smaller than the figure of 96% positive reaction given by Rosenow (1948c). This difference has resulted from the different criteria used for a positive reaction, because the mean reaction given by Rosenow (1948c) of 9·63 cm.² in epileptic patients is within chance variation of the 9·42 cm.² mean of this series. Rosenow (1948c) states without giving statistical data that a reaction greater than 5 cm.² was significant. This is somewhat smaller than the critical figure of 6·05 cm.² found by statistical analysis of my results. However, it must be pointed out that this is a purely arbitrary value derived by mathematical methods which were designed to eliminate the chance inclusion of any normals in the positive group, but, because of the overlap of the amount of reaction in the two groups, some positives will be excluded.

A comparison with some of Rosenow's data is given in Table III.

Effect of Medication.—Almost all the epileptic patients tested were taking medication in the form of either phenobarbitone, diphenylhydantoin (dilantin, epanutin), tridione, or a combination of these drugs. However, a few patients were also taking benzedrine or a bromide, and some were without any medication. No correlation has been found between any one drug or combinations of drugs and the reaction to the intradermal injection of the " epilepsy " antibody.

Epileptic Patients with Negative Reactions to " Epilepsy " Antibody.—A comparison of the clinical picture of the epileptic patients who had negative reactions with the positive group did not reveal any marked difference in sex, age, age of onset, duration of disease, type of seizure, or medication. The interval since the last

TABLE III

A COMPARISON BETWEEN PATIENTS WITH IDIOPATHIC EPILEPSY TESTED BY ROSENOW (U.S.A.) AND THOSE OF THIS STUDY (ENGLAND)

Source	Reaction to Antibodies Isolated from Patients with							
	Epilepsy				Schizophrenia		Arthritis	
	No. Tested	Mean Reaction	Size Reaction Considered Positive	Considered Positive (%)	No. Tested	Mean Reaction	No. Tested	Mean Reaction
Rosenow (personal communication and 1948d) ..	118	9·61 cm.²	5 cm.²	96	118	5·18 cm.²	118	2·45 cm.²
This study (England)	117	9·42 cm.²	6·05 cm.²	78	78	2·40 cm.²	80	2·50 cm.²

seizure before the skin test was made seemed important. The incidence of negative reactions was significantly higher in the group who had not had a seizure for a month or more, and was very low among patients who had had a seizure less than a week before the skin test was done.

The electroencephalograms (EEG) were suggestively better in the negative group, but the number of observations was small and statistically unimportant.

Seven patients had reactions that were significantly negative. As this is about twice the number expected on the basis of a normal distribution, a separate examination of their clinical status was indicated. Three of these patients had normal electroencephalograms, three had generalized EEG abnormalities, and one had not had an EEG. Of the three who had abnormal EEGs, one was dark skinned which makes the skin test difficult, one was a man of 56 with epilepsy of late onset, and one was a boy of seventeen. All these patients were having seizures regularly in spite of medication. The three patients who had negative EEGs had not had any seizures for one month, two years, and eight years respectively. The patient who had not had an EEG had not had a seizure for five years before the skin test was done.

Repeated Tests on the Same Patient.—Three people were tested four, 11, and four times over a period of six weeks. The reaction never varied more than one division on the area measuring device. Several other patients had two skin tests at intervals up to two months. Here again the tests were uniformly similar in result, and only if the reaction was near the critical area was there a variation between positive or negative.

Patients in the Control Group with Seizures.—There were four patients in the control group who were having seizures associated with some known organic disease. Their diagnosis included parietal tuberculoma, pre-senile dementia, hypertensive encephalopathy, and C.N.S. syphilis. All these patients had negative skin reaction to the "epilepsy" antibody. This agrees with Rosenow (1948c).

Patients with Post-Traumatic Epilepsy.—Three patients with post-traumatic epilepsy were tested. One was negative, and two reacted strongly to the "epilepsy" antibody. Each of the positive patients was retested and again found to be positive.

Patients in the Control Group with Positive Reactions.—There were seven patients (6·7%) of the control group without a history of ever having a seizure, but who had positive reactions to the "epilepsy" antibody. Their diagnosis included facial palsy, chronic anxiety

TABLE IV

A COMPARISON OF THE ERYTHEMATOUS REACTION OF A GROUP OF NON-EPILEPTICS LIVING WITH EPILEPTICS AND ONE UNASSOCIATED WITH EPILEPTICS TO ANTIBODIES ISOLATED FROM PATIENTS WITH IDIOPATHIC EPILEPSY

	No. Tested	Reaction to Antibody Isolated from Patients with Idiopathic Epilepsy		Comparison Between Groups		
		No. Positive Reactions	Positive Reactions (%)	Standard Error of Difference	Critical Ratio	Probability
Non-epileptics living with epileptic patients	15	4	26·6	8·2	2·4	·016
Non-epileptic people unassociated with epilepsy ..	105	7	6·7			

state, cerebral thrombosis, traumatic spinal injury, carotid aneurysm, no disease, and hypertensive encephalopathy. The patient who had had a traumatic spinal injury also reacted to the " arthritis " antibody, and the patient with the facial palsy also reacted to the " migraine " antibody. In the other patients the reaction was limited to the " epilepsy " antibody.

Skin Reaction of Families of Epileptic Patients.—The testing of those living with epileptic patients was done on a few people towards the end of the study. A statistically significant increase in the incidence of positive reactions was found among these people as compared to the general control group. If this reaction indicates the presence of a specific organism, particularly one in the nasopharynx, an increased incidence of positive reactions might be expected among people intimately associated with those harbouring the organism.

Table IV gives the precise data.

Discussion

The association of idiopathic epilepsy with a skin reaction to certain alpha streptococci antibodies is definite. However, the meaning of this reaction is not clear. Speculation as to the significance of this test leads immediately to two possibilities: either the alpha streptococcus is aetiologically significant, or the host has a specific effect on the antigenic structure of the organism.

Rosenow (1948c) states that shortly before a seizure, the skin reaction to the epilepsy antibody rises, indicating an increase in circulating antigen; and that directly after a seizure the skin reaction to antibody falls sharply, showing a disappearance of the circulating antigen. He also states that if antigen is used as a skin testing agent, there is often a positive test after a seizure, showing the presence of circulating antibody. This suggests a local sensitization in the brain with circulating antigen as a trigger mechanism. Such a method has been used by Kopeloff and others (Kopeloff, Barrera, and Kopeloff, 1942 and 1944) for the experimental production of epilepsy. Though in the present study insufficient observations were made at or near the time of seizures to shed any light on this question, a definite association was found between the occurrence of seizures and a positive skin reaction to the " epilepsy " antibody.

This study was designed simply to verify the validity of the skin reaction as described by Rosenow (1947b), and no effort was made to investigate the aetiological or pathological significance of the alpha streptococcus in the patients tested. However, the high incidence of positive reactions among people living with epileptic patients suggests a transmissible agent.

Summary

One hundred and seventeen patients with idiopathic epilepsy and 105 non-epileptic patients were tested in England with an intradermal injection of antibodies made in the United States to strains of alpha streptococci isolated from patients in the United States with divers diseases, including idiopathic epilepsy.

The results of the tests have been submitted to statistical analysis which shows the incidence of positive reactions of the epileptic patients to the " epilepsy " antibody to be well beyond any chance variation.

There were 78% positive reactions among the epilepsy patients to the " epilepsy " antibody, and 6·7% positive reactions to this antibody in the control patients. This has been compared with Rosenow's data.

There was definite correlation between the epileptic patients who had negative reactions to the " epilepsy" antibody, normal electroencephalograms, and time since last seizure before the skin test.

All patients with known organic cause for their seizures were negative to the " epilepsy " antibody except two patients with post-traumatic epilepsy.

A statistically higher incidence of positive reaction to the epilepsy antibody was found among non-epileptics living with epileptic patients than in the control group.

No evidence as to the relationship of this reaction to the disease has emerged from this study.

I am glad to have this opportunity to thank Dr. E. A. Carmichael for making this study possible and for his constant encouragement and advice. I also want to thank Dr. E. C. Rosenow for his willing cooperation and for supplying the test materials so liberally.

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LOCAL SIGN IN AUTONOMIC RESPONSES

BY

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There is already an extensive literature on the vascular and sweating responses which are evoked in the limbs by experimental painful stimuli. As far as the present authors are aware, previous investigators are all agreed that these responses show no evidence of " local sign " ; that is to say, a painful stimulus applied to one limb produces an equal response on each side of the body. This point has been studied by Sattler (1943), who also reviewed the previous literature. Sattler, using the Hardy-Wolff stimulator, was unable to find any evidence of local sign in the limbs, either in the vasomotor responses, studied plethysmographically, or in the sudomotor responses, as measured by changes in the skin resistance (psychogalvanic response). He concludes that there is no tendency towards the localization of these responses.

However, as Sattler himself states, there is abundant clinical evidence that localized vasoconstriction does occur in association with painful trauma. Further, Carmichael (1950) has shown that, in subjects with complete transverse spinal lesions, the reflex vasomotor responses to painful stimuli below the level of the lesion are much greater on the ipsilateral side. Similarly, recent work in America, in particular that of Korr (1949), points to segmental differences in sweating patterns in pathological conditions. Korr finds cutaneous areas of increased sweating which are segmentally related either to diseased viscera or to skeletal damage. It seems clear, therefore, that local reflex pathways do exist, and there is no *a priori* reason why their function should not be demonstrated in the healthy human subject. There is some reason to believe that, in the intact and conscious subject, autonomic responses to painful stimuli derive not only from local reflex activity at the spinal level, but also from higher centres whose function may correlate with the subjective experience of emotion. Investigators are generally agreed, for example, that the unfulfilled threat of injury may produce a greater degree of vasoconstriction or sudomotor activity than the injury itself. If it is assumed that the autonomic response associated with emotion is in the nature of the diffuse " fight or flight reaction " described by Cannon, and is without lateral sign, then a painful stimulus may be sufficiently disturbing to arouse a diffuse " emotional " response involving widespread vasoconstriction and increased sweating, which will overlie the comparatively small spinal reflex. It is this spinal reflex which might be assumed to mediate local sign.

In order, therefore, to demonstrate local sign, it would appear necessary to reduce the autonomic disturbances brought about by psychological reaction to as low a level as possible. Thus it is preferable to use " test sophisticated " subjects able to adopt an attitude of indifference to painful stimuli. Further, it is possible that the nature of the painful stimulus can also affect the demonstration of local sign. A sharp cutaneous pain may produce a large psychological response without much local activity, whereas a " dull " pain, resulting from deep stimulation, may produce a smaller psychological response but more local reflex activity.

In the present paper it is shown that, if attention is given to the considerations mentioned above, it is possible to demonstrate local sign. That is to say, if a painful stimulus is applied to either limb, an autonomic response is obtained which is comparatively greater on the ipsilateral side.

During preliminary investigations into the value of the psychogalvanic response for studying variations in autonomic function, local sign appeared to be present, and it was decided to repeat these experiments in a form suitable for precise analysis. This was done in the case of three healthy adult subjects. It was thought advisable to confirm the results obtained with these three subjects in other, less sophisticated, subjects.

Accordingly, the records of certain patients who had undergone bilateral stimulation and recording were analysed. The only criterion in the selection of these records was that they should be suitable for analysis. That is to say, every experiment is reported in which the presence or absence of local sign can be tested by statistical analysis.

Finally, the experiment was repeated plethysmographically, thus verifying that local sign was not an artefact of the electrical method of recording and stimulation. This procedure also has the advantage of demonstrating local sign in vasomotor as opposed to sudomotor responses.

Methods

Method 1 : Skin Resistance Technique.—The response recorded was the fall in skin resistance which followed the stimulus described below. These responses were measured from both sides of the body simultaneously on independent A.C. circuits of the type described by David Grant (1946). The subject was seated comfortably with the arms on arm rests, thus maintaining as far as possible equal conditions of posture and relaxation for each limb. Plain copper electrodes of 13 mm. diameter were lightly attached by rubber retaining straps to the pulp of the tips of digits 2 and 4 of each hand. Changes in the electrical resistance between these electrodes were recorded simultaneously in each hand with mirror galvanometers reflecting a focused beam of light onto moving photographic paper. The apparatus was of the constant current type, and the use of 50 cycle A.C. reduced variability in the recorded responses resulting from polarization, and enabled plain copper electrodes to be used. The sensitivity of the apparatus was calibrated so that the skin resistance changes could be measured in ohms. A photographic record of respiration was made simultaneously by means of a focused beam of light reflected from a chip mirror attached to a rubber tambour. It was thus possible to take account of responses resulting from irregular deep respirations, rather than from the experimental stimuli.

It is not the purpose of this paper to discuss the physiology of skin resistance, but it should be mentioned that the changes which occur are generally admitted to reflect alterations in autonomic tone, and most workers agree that these changes probably indicate alterations in sweating activity (McCleary, 1950).

In method 1, the stimulus was a square wave from an Ediswan electrical stimulator. The stimulus was applied to the pulp of the little finger by means of a plain copper electrode of the type used for recording. Each hand was stimulated separately. A saline pad attached to the leg acted as an indifferent electrode earthing the subject to the stimulating apparatus. The duration of the stimulus was controlled mechanically and was constant at 400 m. sec. The pulse duration was 1 m. sec. and the pulse frequency was 100 cycles per sec. A shock artefact appears in the photographic record but it can be seen that this is complete within the latent period of the autonomic response (Fig. 4). The intensity of the stimulus varied from subject to subject, but was usually at the minimum level which gave easily measurable responses. When the strength of the stimulus varied within one experimental session, the responses resulting from these different stimulus intensities were nevertheless used, as this source of variability is allowed for in the method of analysis. An equal number of stimuli was applied to each side of the body, and the stimuli on each side were evenly distributed over the time series. Further, responses were recorded on both possible circuit arrangements. That is to say, recordings were made of responses from the left hand on circuit A, and those from the right hand on circuit B ; and responses from the left hand on circuit B, and those from the right hand on circuit A. The recording circuits could be changed with respect to the two hands by means of switches and without removing and replacing electrodes. The purpose of this procedure was to enable separate estimates to be made of variability in responses attributable to a difference in the two circuits, and variability attributable to different reactivity of the two sides of the body.

Three healthy adults and ten patients suffering from irrelevant neurological disorders served as subjects for the experiments using method 1.

Method 2 : Plethysmographic Technique.—The response recorded was the diminution in finger volume which followed the stimulus. The technique has been described previously by Bolton, Carmichael, and Stürup (1936). The subject was seated as for method 1, except that in order to attain the maximum vasodilatation the subject's legs were immersed in water kept at a temperature of 44° C. Glass plethysmographs were placed over the third digit of each hand, and sealed with zinc oxide paste, care being taken to ensure that no venous occlusion occurred. Changes in the volume of the finger were recorded optically on moving photographic paper through the medium of mirrors attached to tambours, which were connected to the glass plethysmographs by a closed air conducting system. Although an approximately equal volume of the finger was included in the plethysmograph on each side, no attempt was made to measure this volume exactly. Nor was the recording system calibrated volumetrically. However the sensitivity of the circuits was adjusted by moving the tambour relative to the focused beam of light and the recording screen, so that a deep inspiration produced approximately equal deflections of the two recording light beams. Respiration was recorded as in method 1.

In method 2 the stimulus was squeezing of the muscles at the back of the neck.

Two healthy adults, who also served as subjects in method 1, served as subjects in method 2.

The Design of the Experiment

Local sign is often apparent from a careful inspection of the raw data, but in order to demonstrate unequivocally the presence of local sign in autonomic responses, a method of analysis of results is required which will give the level of confidence at which local sign can be said to be present.

It is important that all other factors which could influence the results should be held constant. A degree of control which will define the contributions to the final result made by each experimental variable, and by interactions between these variables, is provided in the methods of analysis of variance. Accordingly, in the case of method 1, we employed a three factor analysis of variance with replication, and in the case of method 2, a two factor analysis with replication (Brownlee, 1949).

Method 1.—In the case of the skin resistance technique the factors isolated as sources of variability in the size of autonomic responses are : (*a*) the side of the body stimulated, left or right ; (*b*) the circuit on which the response is recorded (the two circuits were changed with respect to the two hands at intervals during the experiment) ; (*c*) the side of the body, left or right, from which the response is recorded.

Estimates are also made of variability resulting from interaction between each pair of these factors, i.e., between (*a*) and (*b*) ; between (*a*) and (*c*) ; and between (*b*) and (*c*). If there is a significant interaction between factors (*a*) and (*c*), that is to say between the side of the body stimulated, left or right, and the side of the body, left or right, from which the response is recorded, as factors affecting the size of recorded responses, then local sign is significantly present. It is to be noted that other irrelevant variables such as a difference in the sensitivity of the two circuits, or a time series effect resulting from practice or from a change in the strength of the stimulus, are either independently assessed as sources of variability, or appear in the residual variance against which variance attributable to local sign is tested.

A requirement of this three factor method of analysis is that an equal number of recordings from each side of the body should be made on each circuit, and that an equal number of stimuli on each side of the body should be applied for the recording from each side on each circuit. This calls for a basic block of eight recorded responses, which may be replicated any number of times in any one experiment. In the experiments using method 1, the number of replications varied from two to 12. Whenever a change in the stimulating voltage occurred during one experiment, it occurred with a change in circuits or between one replication and another, but never in such a way that an artefactual interaction between any pair of the three main factors could be involved.

Method 2.—In the plethysmographic experiments, the recording circuits were not changed with respect to the two hands, and so variability resulting from differences in reactivity of the two sides of the body, and variability resulting from differences in the sensitivity of the recording circuits, could not be separated. However, these two sources of variability are together a constant factor which is extracted by the method of analysis, and could not produce artefactual local sign. A two-factor analysis with replication was therefore applied to the results obtained with the plethysmographic technique and the two factors isolated were the compound factor already mentioned of the circuit on which the recording was made, and the side of the body from which the recording was obtained ; and the side of the body stimulated, left or right.

A significant interaction between these two factors provides evidence of local sign in vasomotor responses. In a simple two factor analysis it is not possible to isolate this interaction, which would appear in the residual variance, but when the additional factor of replication is introduced this first order interaction can be isolated. Accordingly, in the plethysmographic experiment reported here the basic block of four recorded responses required by the two factor analysis has been replicated twelve times.

Results

Method 1.—An analysis of the responses of the three healthy subjects (M.A.C., A.E., and M.P.) for the skin resistance experiments showed local sign to be present, according to the criterion discussed above, at the 0·001, 0·01 and 0·05 levels of confidence respectively (Table I).

Of the 10 patients whose records were suitable for analysis by the three factor method, three showed local sign, one at the 0·001 level of confidence, one at the 0·01 level, and one at the 0·05 level (Table II). Of the remaining seven subjects in whom local sign was not present at a statistically significant level, inspection of the raw data shows the effect (relationship between the side stimulated and the side giving the larger response) to be in the direction required by the hypothesis of local sign in every case (Table II). It should be mentioned that in the case of those subjects who showed local sign to a statistically significant degree, the analysis of variance does not itself give any indication of the direction of the effect but inspection of the original data makes it clear that the direction of the effect is according to hypothesis.

Method 2.—Of the two experiments using the technique of plethysmography, one was a failure, since the maximum practicable vasodilatation resulted in recorded responses which were too small to be measured or compared. The other, however, yielded a highly significant result. A two factor analysis with replication carried out on the results from this subject showed local sign to be present at the 0·01 level of confidence (Table III). The interaction in question just misses the 0·001 level of significance.

The results of this experiment, and the results of the skin resistance experiment on subject M.A.C., are also presented graphically. In Figs. 1 and 2, the ordinate and abcissa represent the size of the response from the left and the right sides of the body respectively. An indication is thus given of the ratio of the responses from each side of the body

TABLE IA

LOCAL SIGN IN SKIN RESISTANCE CHANGES FOLLOWING PAINFUL STIMULI IN THREE HEALTHY SUBJECTS (MEAN RESPONSES)

Side of Response	Left		Right		Number of Replications (N)
Side Stimulated	Left	Right	Left	Right	
Subject M.A.C.					
Circuit A	5·9	2·6	3·7	7·2	7
Circuit B	5·3	1·8	3·4	6·5	
Subject A.E.					
Circuit A	7·2	7·9	5·0	9·2	12
Circuit B	7·8	7·7	5·0	7·5	
Subject M.P.					
Circuit A	10·3	8·0	5·2	6·9	7
Circuit B	6·8	5·0	5·8	7·1	

The actual recorded responses are not shown. The figures shown above give the mean value in ohms $\times 10^3$ of the responses obtained following stimulation on each side of the body. Figures under (N) refer to the number of replications, and indicate the number of observations from which each mean was calculated. The individual responses in subject M.A.C. are presented graphically in Fig. 3.

TABLE IB

LOCAL SIGN IN SKIN RESISTANCE CHANGES FOLLOWING PAINFUL STIMULI IN THREE HEALTHY SUBJECTS

Subject	M.A.C.			A.E.			M.P.		
Source of Variance	Degrees of Freedom	Mean Squares	P	Degrees of Freedom	Mean Squares	P	Degrees of Freedom	Mean Squares	P
Circuit (C) ..	1	4·5714	—	1	2·1600	—	1	29·0016	—
Side of Response (R) ..	1	23·1429	—	1	21·8504	—	1	21·5106	—
Side Stimulated (S) ..	1	0·0257	—	1	79·2066	—	1	0·9516	—
C × R	1	0·2579	—	1	6·7204	—	1	47·3616	0·05
C × S	1	0·3151	—	1	10·1400	—	1	0·0045	—
S × R .. Local Sign	1	159·8064	0·001	1	55·5105	0·01	1	44·1087	0·05
C × R × S	1	0·0113	—	1	1·1704	—	1	0·5716	—
Replication Factor ..	6	24·8053		11	76·6558		6	36·7348	
Residual	42	7·7728		77	7·5998		42	8·0952	

The raw data for this analysis (three factor analysis with replication) are the responses whose means are shown in Table IA. No estimation has been made of the significance of the replication factor, but all other factors and interactions significant at the 0·05 level and above are shown in the column headed P. The significant interaction between the circuit factor and the side of the response in subject M.P. results from the two possible arrangements of the circuits with respect to the sides of the body being unevenly distributed over the time series.

by the position of each symbol relative to the co-ordinates. The side of stimulation is indicated for each pair of responses. The distribution of the responses shows clearly the influence of the side of stimulation on the relative size of responses from the left and right sides of the body. It can also be seen that the responses to a deep inspiration are intermediate between those to stimulation of the left side of the body and those to stimulation of the right. A series of actual recorded responses are reproduced in Figs. 3 and 4.

Discussion

In the five experiments on healthy subjects (three skin resistance experiments, and two plethysmographic experiments) the attempt has been made to minimize conditions which would be likely to mask local sign. At the same time a method of analysis was used that would give results which, if positive, would provide unequivocal evidence of local sign. This attempt has been successful in all but one of our experiments on healthy subjects (the plethysmographic experiment on subject M.P.). The failure in

TABLE II

LOCAL SIGN IN SKIN RESISTANCE CHANGES FOLLOWING PAINFUL STIMULI IN TEN HOSPITAL PATIENTS

Subject	Mean Response on Left		Mean Response on Right		Number of Replications (N)	Level of Significance of Local Sign
	Left Side Stimulated	Right Side Stimulated	Left Side Stimulated	Right Side Stimulated		
E.S.	14·9	11·8	7·9	9·6	7	0·001
J.B.	8·1	3·7	4·1	3·3	4	0·01
C.J.	18·1	16·6	12·6	15·6	5	0·05
H.W.	2·0	1·5	1·6	2·1	4	—
D.R.	3·7	3·0	3·8	4·4	4	—
F.C.	15·3	15·6	7·9	12·6	3	—
H.S.	1·4	1·8	0·2	1·3	2	—
E.R.	10·8	8·1	10·0	9·4	7	—
E.C.	19·1	14·2	20·9	19·9	3	0·2
S.T.	2·1	1·4	2·3	1·8	3	—

The analysis of variance was a three factor analysis with replication resembling in all respects that shown in Table I. The figures given are the mean values in ohms $\times 10^3$ of the responses from each subject. The number of observations from which the mean is calculated is given in the column headed (N).

The level of significance refers to the interaction between the factor for the side of the body stimulated and the factor for the side of the body from which the response is recorded. The level of significance is indicated for each subject in which local sign reaches the 0·2 level or above.

TABLE III

LOCAL SIGN IN VASOMOTOR RESPONSES TO PAINFUL STIMULI

Subject		A.E.			
Side of Response		Left		Right	
Side Stimulated		Left	Right	Left	Right
Replications	1	3·2	1·8	1·6	0·6
	2	3·5	1·4	3·2	1·8
	3	4·9	1·3	2·6	4·6
	4	3·2	2·7	1·9	5·2
	5	1·0	2·7	0·3	4·2
	6	3·9	1·2	1·0	1·3
	7	1·1	0·3	0·5	1·6
	8	1·2	1·1	1·0	2·4
	9	2·2	0·9	0·7	0·8
	10	2·2	0·9	2·3	2·9
	11	2·9	1·0	2·2	3·0
	12	3·0	1·5	2·8	3·3
Total Response		32·3	16·8	20·1	31·7
Mean Response		2·7	1·4	1·7	2·6

Source of Variance	Degrees of Freedom	Mean Squares	Level of Significance
Side of Response (R)	1	0·1519	—
Side Stimulated (S)	1	0·3169	—
R × S .. .. Local Sign ..	1	15·3002	0·01
Replication Factor	11	1·4335	
Residual	33	1·2270	

In this table the size of the responses measured in cm. on the record are given in full together with the analysis of variance (two factor analysis with replication).

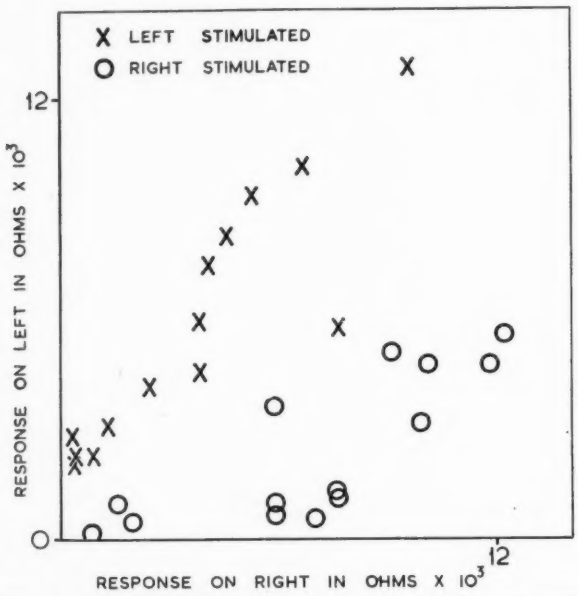

FIG. 1.—Graphic representation of local sign in skin resistance changes (method 1) following painful stimuli. The autonomic responses represented here are the raw data on subject M.A.C. analysed in Table I. The circuit on which each response is recorded is not shown here but the side stimulated is indicated by a symbol, and the size of the response on each side of the body is shown by the position of the symbol in relation to the coordinates.

this case can be attributed to recorded responses too small for measurement and comparison, resulting from inadequate vasodilatation. In the case of our less sophisticated subjects, only three out of 10 experiments gave results unequivocally supporting the hypothesis of local sign.

Previous failures to demonstrate local sign in the sweating and vasomotor responses to painful stimuli, and our own difficulty in demonstrating the effect in hospital patients, seems largely due to the difficulty of controlling the subject's attitude. Our three healthy subjects had had previous experience of similar experimental situations and were, of all our subjects, almost certainly the least disturbed emotionally by the conditions of the investigation. It would seem important for the demonstration of local sign in autonomic responses, that the comparatively simple reflex response to pain should be overlaid or modified as little as possible by any diffuse autonomic activity, appearing as a concomitant of emotion. Thus the subject should not be startled by or made apprehensive of the stimuli, and the stimuli themselves should not be near the limit of the subject's tolerance, although, of course, they must be sufficiently intense to produce measurable responses even after some habituation.

The nature of the stimulus used in this type of experiment calls for brief comment. During the preliminary investigations, several different types of stimuli were used. No local sign was apparent in the responses to pin-prick or to pinching a small fold of skin. It was noted also that in the case of these stimuli there was a sharp decrease in the intensity of the response with repetition of the stimulus. It is presumed that a response which habituates so readily is largely in the nature of a startle reaction. Local sign did appear to be present, however, when the stimulus was squeezing of a larger volume of tissue including muscle (biceps, lower edge of pectoralis major, and the muscles at the back of the neck). Moreover, responses to this type of stimulus showed comparatively little habituation. The superiority of this type of stimulation may be due simply to the greater area of tissue stimulated as opposed to any qualitative differences associated with the particular receptors involved.

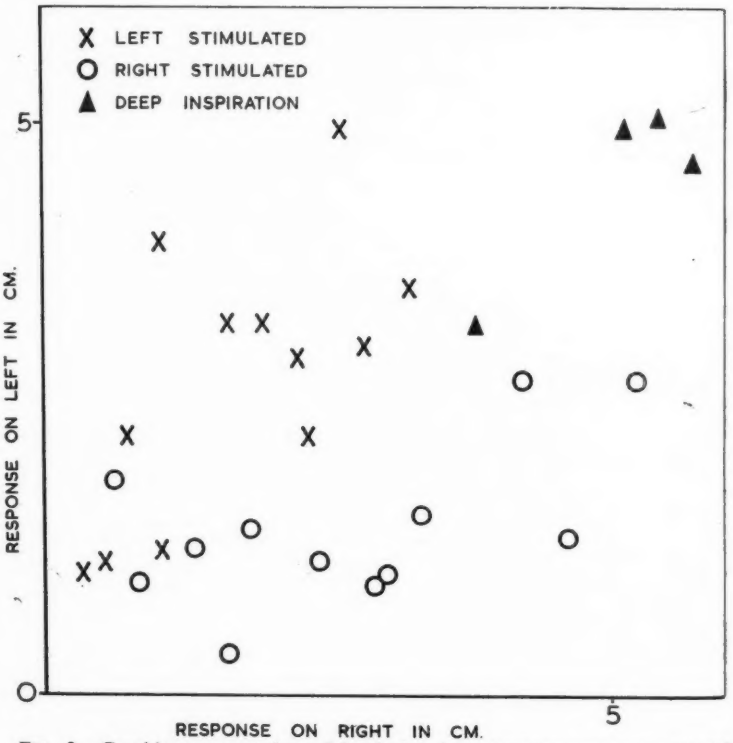

FIG. 2.—Graphic representation of local sign in vasomotor responses recorded plethysmographically (in subject A.E.). The responses to painful stimuli represented here are the raw data of the analysis shown in Table III. The side stimulated is indicated by a symbol and the side of the response on each side of the body is shown by the position of the symbol in relation to the coordinates. Responses to deep inspirations are also shown.

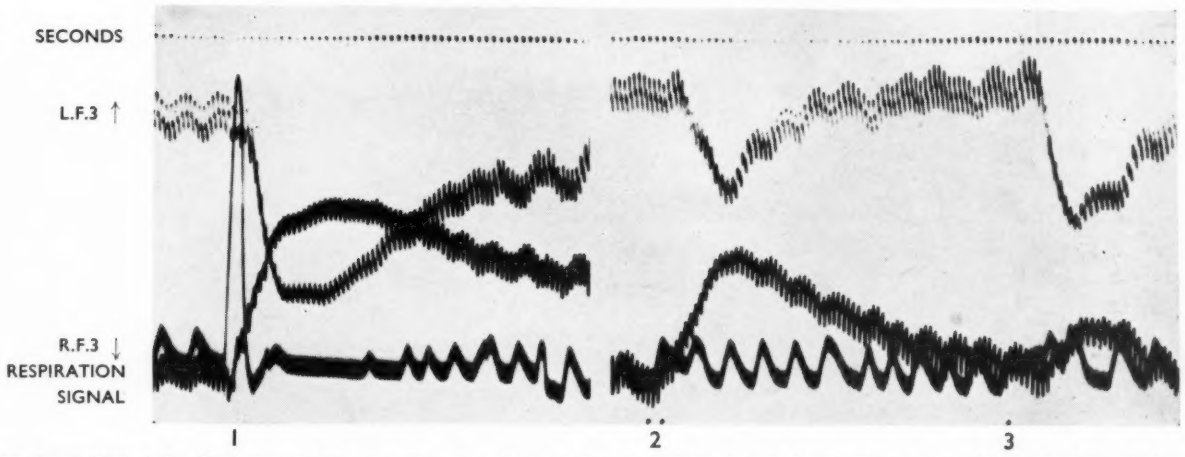

FIG. 3.—Subject A.E. Plethysmographic recording of vasoconstriction in digit 3 of each hand. Response to (1) maximal inspiration, (2) stimulus on the right, (3) stimulus on the left. Recording systems adjusted so that the response to a deep breath gives approximately equal deflections on the two sides. Stimuli for responses (2) and (3) : painful pressure on the posterior muscles of the neck at the level of the seventh cervical vertebra. Vasoconstriction is greater on the side stimulated. The arrows indicate increase in volume of the third finger of each hand (L.F.3 and R.F.3).

The results reported here were obtained only with stimuli which were painful. However, it is clear that other sensory modalities were involved (e.g., proprioceptive), and we have no definite evidence that the afferent fibres mediating the reflex were those subserving pain.

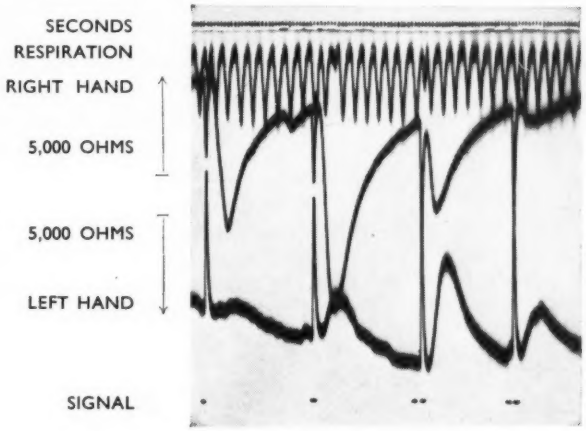

FIG. 4.—Subject M.A.C. Changes in skin resistance following electrical stimulation of the pulp of digit 5 of each hand. Each shock is marked by a large stimulus artefact. The first two shocks are on the right, and the third and fourth on the left. The fall in skin resistance is greater on the side stimulated. Stimulus, 70 volts in each case, pulse duration 1·0 m/s., frequency 100 c/s., duration 400 m/s. The arrows indicate direction of a rise in skin resistance, and also show the excursion corresponding to a change in resistance of 5,000 ohms.

Summary

Autonomic responses to painful stimuli in the upper limbs have been studied, using skin resistance and plethysmographic techniques. It has been shown that, when the attitude of the subject can be suitably controlled, it is possible to demonstrate local differences in the autonomic responses to painful stimuli which are anatomically related to the site of stimulation.

Previous failures to detect this effect are discussed.

We wish to record our thanks to Dr. E. A. Carmichael and Mr. O. L. Zangwill for their encouragement and helpful suggestions. We wish also to express our gratitude to the medical staff of the National Hospital for their courtesy in allowing us to examine patients under their care.

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SUBACUTE NECROTIZING ENCEPHALOMYELOPATHY IN AN INFANT

BY

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The following case appears to be unique in that no references to a similar condition can be found in the literature. In addition it merits consideration as an example of the reaction of the infant brain to disease.

Case Report

K.H., a boy, aged 7 months 3 weeks, was admitted to King's College Hospital on April 22, 1947.

Birth had been normal (birth weight $6\frac{3}{4}$ lb.) as also was development until six weeks before admission. The infant was vaccinated at the age of 2 months. He was breast-fed entirely for six weeks, then complementary feeding was begun.

The baby's behaviour was normal until six weeks before admission when he stopped crying, lay very still, and slept for long periods, only waking when disturbed. He did not suck and had to be fed by spoon. Sweating was increased during this period.

He had had no specific fevers.

There was one sister aged 10. At the onset of the baby's illness this sister was at home with a cold, sneezing and coughing a good deal.

On examination it was seen that the general nutrition was good, the skin normal, and the mouth and throat healthy. There was no glandular enlargement, and no palpable enlargement of liver or spleen. There was no abnormality in heart or lungs.

The pupils were small with no reaction to light, or appreciation of light; ophthalmoscopy showed a bilateral optic atrophy, with normal maculae and retina. The infant appeared to be deaf. No other abnormality was observed in the cranial nerves. Both upper and lower limbs were markedly spastic. Reflexes were not obtained. There were bilateral extensor responses.

Investigations.—Lumbar puncture was performed on April 22 and 10 ml. fluid removed under increased pressure. Analysis showed cells 2 per c.mm.; protein 30 mg. per 100 c.mm.; globulin, negative; sugar present; chloride 740 mg. per 100 c.mm. Lange curve 0111000000; Wassermann reaction negative.

On April 23 a radiograph of the chest showed no abnormality.

The child became rapidly worse, and on April 25 was comatose, dying in terminal hyperpyrexia later the same day.

The clinical diagnosis was obscure, but an encephalitic process was considered to be the most likely cause of the fatal illness.

Necropsy.—A necropsy was performed 69 hours after death. No abnormality was observed except in the central nervous system.

The brain weighed 740 g. There was a severe, diffuse vascular injection of the leptomeninges. The convolutions were normal in size and appearance. In coronal sections the cerebral white matter seemed somewhat greyer than normal. The left lateral ventricle was slightly dilated. The caudate and lenticular nuclei appeared normal. Mid-thalamic sections showed areas of dark grey-brown discoloration involving the anterior nucleus, dorsomedial nucleus, nucleus submedius, zona incerta, and substantia nigra on both sides. More posteriorly the lesions were limited to the medial third of the pulvinar on either side. In the midbrain similar greyish-brown areas occupied the whole tegmentum; at the level of the inferior colliculus and upper pons the process was confined to the central region between the inferior colliculi and the trapezoid bodies. In the midpons the lesion was most marked in the region of the trigeminal motor nuclei. The upper medulla showed a most striking bilaterally symmetrical red-brown discoloration of the inferior olivary nuclei; in the lower medulla the whole of the central grey matter was similarly affected. In the spinal cord this dark red-brown appearance was seen in the posterior columns, particularly in their medial parts. The cervical region was more affected than the thoracic, whilst the lumbar segments did not show this change.

Microscopic Findings.—Histologically all the areas which showed macroscopic change were the site of a profuse proliferation of the smaller blood vessels, capillaries, pre-capillaries, arterioles, and venules (Fig. 1). The walls of these vessels were not thickened and in none was there either thrombosis or haemorrhage. In the situations where this vascular proliferation was present, the nerve cells were often severely damaged, showing a variety of degenerative changes.

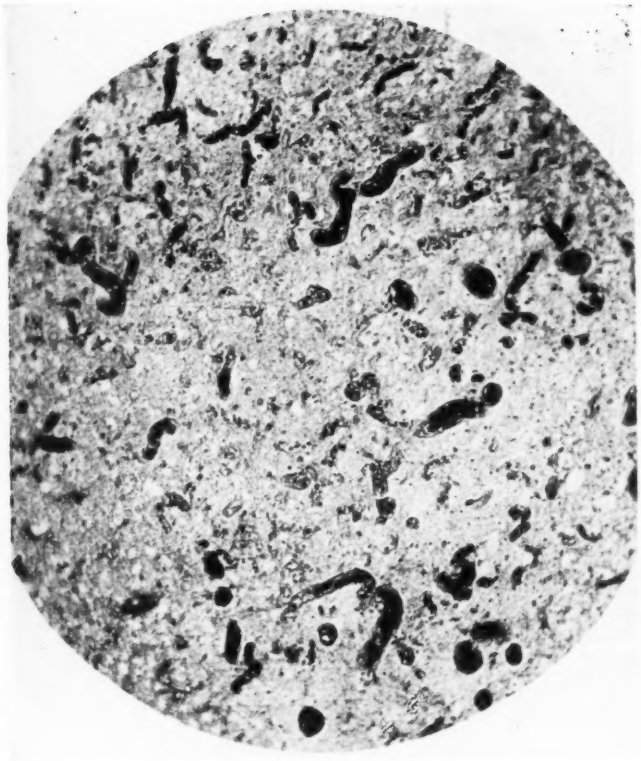


FIG. 1.

FIG. 1.—Vascular proliferation in the anterior nucleus of the thalamus. Perdrau's silver stain × 90.

FIG. 3.

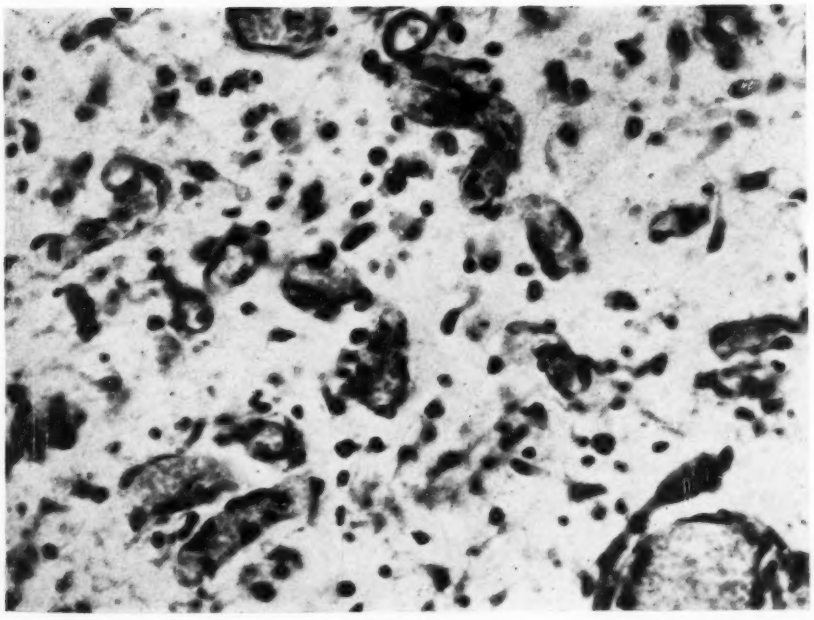
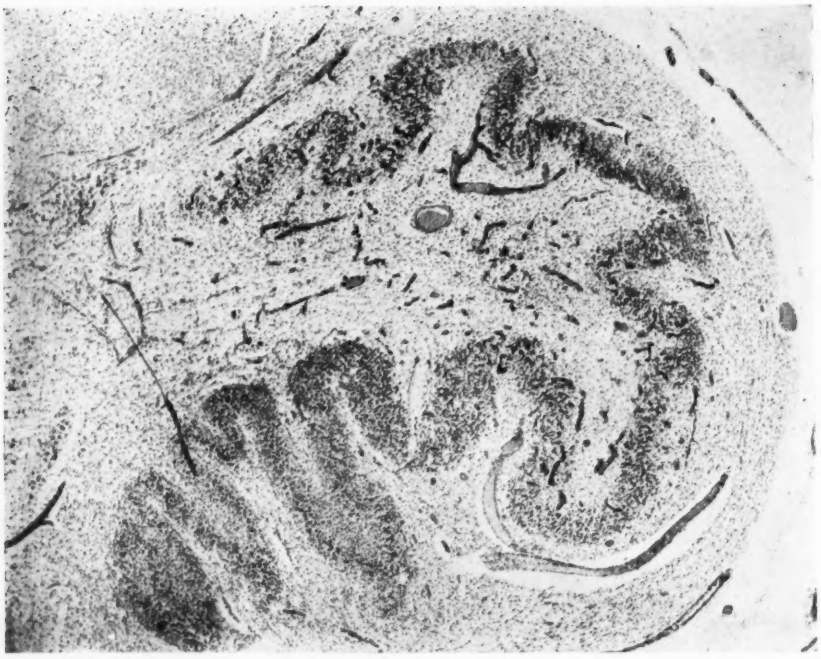


FIG. 2.

FIG. 2.—Periaqueductal grey matter of the mid-brain, showing microglial proliferation, compound granular cells, and a proliferation of capillaries and precapillaries. Nissl × 350.

FIG. 3.—Thalamus at mid-dorsal level, showing destruction particularly of the anterior nucleus, nucleus magnocellularis, and the midline nuclei. Note sparing of subthalamic nucleus (corpus Luysii). Heidenhain's myelin stain × 2.



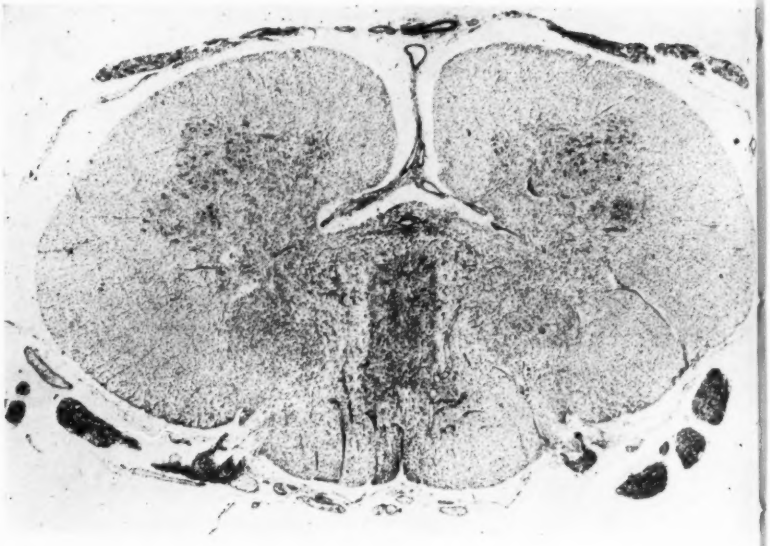


FIG. 4.—Inferior olive showing preservation of the dorso-medial portion of the nucleus. An intense glio-mesodermal reaction, with destruction of olivary nerve cells, can be seen in the dorso-lateral and ventral portion of the olive. Nissl × 20.

FIG. 5.—Spinal cord, fifth cervical segment. Vascular and glial proliferation in the columns of Goll. Nissl × 11.5.

FIG. 6.—The same cord segment showing gliosis of the dorsal portions of the posterior columns and around the central canal. Holzer × 11.5.

These included swelling of the cell body with central chromatolysis and nuclear swelling, general cell shrinkage, neuronophagia, and satellitosis. Normal neurons were also present, however, and the nerve cell changes were by no means as prominent as the vascular proliferation. The microglia was extremely active, all forms of transitional types being seen, up to the fully developed compound granular cell. The latter were grouped chiefly at the periphery of the lesion, often in great number. There was a considerable reduction in the number of oligodendrocytes and a general loosening of the interstitial tissue. A marked macroglial proliferation was observed both in Nissl and Holzer preparations. The general appearance of the lesion is shown in Fig. 2.

The thalamus was severely affected, particularly the anterior nucleus, nucleus magnocellularis of the dorsalis medius, and the mid-line nuclei. The parvo-cellular part of the nucleus dorsalis medius, lateralis posterior, and ventralis medalis posterior showed many of the above changes, but of less intensity, whilst the reticular and adjacent ventralis posterior lateralis, paralamellar and lateralis dorsalis nuclei, although involved, showed the mildest change. Sections stained for myelin by Heidenhain's method showed a demyelination in the regions of these nuclei (Fig. 3). The anterior thalamic radiation was also demyelinated. The optic nerves were demyelinated. Holzer preparation revealed a conspicuous gliosis in the internal capsule, in the anterior thalamic radiation, subcallosal fasciculus, optic tract, and in the septum between the fornix and the corpus callosum. There was also a subependymal gliosis of moderate degree. It was noteworthy that both the mammillary bodies, and the subthalamic body of Luys were completely unaffected. In the region of Forel's field were two bilaterally symmetrical softenings measuring 2–3 mm., with many compound granular and microglial cells and an intense proliferation of blood vessels, chiefly capillaries.

In the midbrain there was much destruction. The red nuclei were severely involved throughout their whole extent, as were the oculo-motor nuclei. The corpora quadrigemina showed patchy areas of destruction, the inferior corpus quadrigeminus being the most seriously damaged. The substantia nigra was severely affected in its lower third, the upper two-thirds of the nucleus giving a normal histological appearance. The symmetry of the lesions was remarkable, identical fields being involved on both sides. The Holzer technique showed a gliosis in the region of the red nucleus, and a heavy gliosis of the intramesencephalic course of the oculomotor nerve. There was in addition a subependymal gliosis of mild degree.

In the pons the same process was seen, occupying that portion of the pons dorsal to the trapezoid fibres and ventral to the aqueduct and upper portion of the fourth ventricle. It was remarkable that amidst this area of destruction the neurons of the trochlear nuclei stood out intact.

In the medulla a remarkable shift of the process had occurred, the inferior olives alone being affected. The dorsomedial aspects of the olives were well preserved, but the remainder of the nucleus was severely damaged. Practically the whole of the hilus was occupied by a vascular proliferation of capillaries, pre-capillaries, arterioles, and dilated venules (Fig. 4). There was, in Holzer preparations, a moderate fibrous gliosis both of the inferior olives, and of the subependymal layer. Heidenhain preparation showed a demyelination of the white matter in the hilus of the inferior olives.

In the spinal cord the lesion was confined to the dorsal columns. In the cervical region the anterior horn cells were quite normal. The dorsal columns, particularly the gracile fasciculi, were the site of a pronounced glio-mesodermal reaction (Fig. 5). Holzer sections revealed a fibrous gliosis of the dorsal portions of the posterior columns and around the central canal (Fig. 6). Heidenhain staining showed a demyelination within the affected areas. In the thoracic region the same process could be seen, but it was clearly diminishing in intensity until in the lumbar region no abnormality could anywhere be detected.

No microscopic abnormality of the meninges, meningeal blood vessels, cerebral or spinal blood vessels, apart from the changes described, was anywhere detected. The remainder of the central nervous system was within normal limits for an infant of 31 weeks.

Discussion

The extent of the lesions is represented diagrammatically in Fig. 7. The changes were bilaterally symmetrical extending from the thalamus to the thoracic cord, and their localization obviously accounted well for the clinical picture of drowsiness, blindness, deafness, and spasticity of the limbs.

Microscopically, the lesions collectively were remarkably similar in appearance, consisting of areas of softening and an intense glio-mesodermal proliferation. The vascular overgrowth was the most striking feature, but it was noticeable that elsewhere throughout the central nervous system the vessels were entirely normal. This vascular reaction was so intense as to be out of all proportion to the extent of nerve cell damage. The changes in the latter ranged from acute cell swelling and central chromatolysis to complete destruction, and the interstitial tissue (ground substance or neurophil) was loosened, or completely broken down. Of the glial elements the astrocytes had proliferated, and in certain areas had produced a well marked fibrous gliosis. The microglia was extremely active, all forms of transitional cell types being present, up to the fully developed compound granular cell.

The remarkable localization of the lesions immediately poses the problems of pathogenesis and diagnosis. The resemblance of the pathological changes to those found in subacute necrotic myelitis was impressive at first glance. However, in all cases of the latter condition described to date the process has been confined to the spinal cord,

and to adults, usually in their fourth or fifth decades. The clinical picture of progressive amyotrophic paraplegia, with dissociated sensory changes,

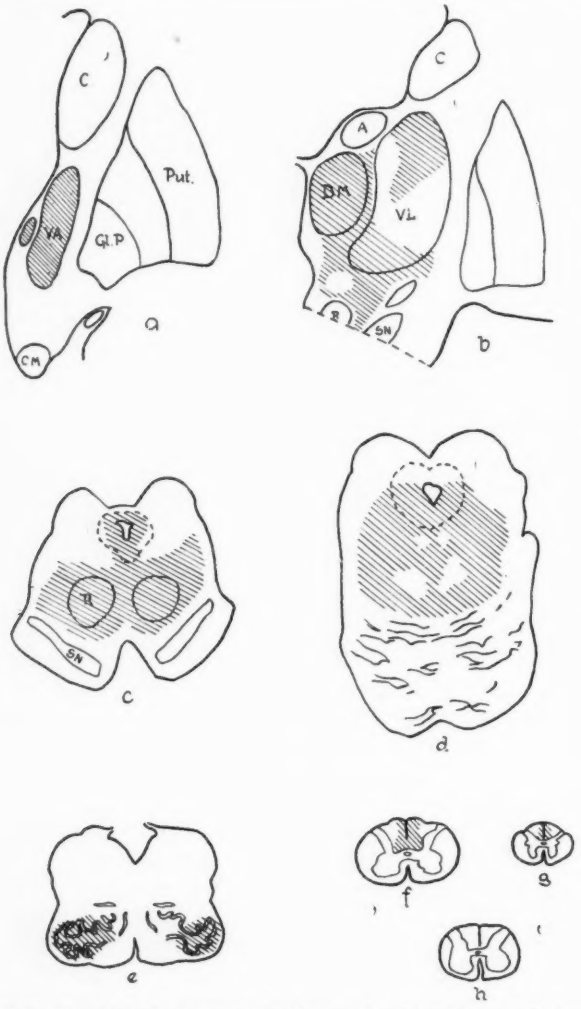


FIG. 7.—Hatched areas indicate the situations of the lesions at various coronal levels of the thalamus, brain stem, and spinal cord.

loss of tendon reflexes and of sphincter control, together with the increased cerebrospinal fluid protein, and a subacute course is very different from that presented in the patient reported here. Again, the pathological findings in this condition of a vascular overgrowth and a primary obliterative sclerosis of small intramedullary and meningeal vessels together with great thickening of the walls of the larger arteries (Greenfield and Turner, 1939) are quite distinct from the pathological appearances in the present case. Similarly, angioma racemosum venosum, which Wyburn-Mason (1943) considers to be identical with subacute necrotic myelitis, may be dismissed, as in no case has such a condition affected the nervous system above D5–D6 spinal segments.

The acute necrotizing haemorrhagic encephalopathy recently described by Adams, Cammermeyer, and Denny-Brown (1949), equine encephalitis and arsenical encephalopathy in no wise resemble this case pathologically, for in all inflammatory and haemorrhagic reactions are outspoken.

There is, however, a striking similarity between the tissue reaction here and that found in the Wernicke syndrome. There is the same vascular proliferation, the same local nerve cell changes and the same reactive proliferation of microglial and astrocytic elements. Although acute perivascular haemorrhages are common, as described by Wernicke (1881) and other authors (Spillane, 1947), nevertheless they are not invariable (Meyer, 1944). But in the Wernicke syndrome the mammillary bodies and other hypothalamic nuclei, periventricular part of medial thalamic nuclei, oculomotor nuclei, superior and inferior colliculi, periaqueductal grey matter, dorsal medulla and olives usually bear the brunt of the condition (Spillane, 1947). In this infant the mammillary bodies were not affected, and spinal cord lesions are unusual in Wernicke cases, although Bender and Schilder (1933) have described haemorrhages around Clarke's nucleus and around the lateral horns in the cervical region. The remaining lesions, however, are in situations commonly affected in the Wernicke syndrome.

The question arises as to whether this is the reaction of an immature brain to the same type of nutritional deficiency producing the Wernicke syndrome in the adult. Experimentally, the work of Ferraro and Roizin (1942) lends some weight to the suggestion that this may indeed be the case. These authors studied the neuropathological changes resulting from acute experimental inanition in the cat. Following complete deprivation of both food and water, death occurred from seven to 64 days later. In the brain two types of histological change were observed ; on the one hand nerve cell changes ranging from a diffuse chromatolysis, with nuclear pyknosis, to a widespread ischaemic cell change, and on the other hand, progressive vascular changes. These latter included a "moderate process of endarteritis" with hypertrophy and hyperplasia of endothelial cells, and a proliferation of the capillaries and pre-capillaries. In the region where this change was most marked, the astrocytes were generally larger and more numerous than usual. The localization was of interest, the cortex, subcortical areas, hypothalamus, lateral geniculate body, corpora quadrigemina, vestibular nuclei and inferior olives all being affected. These workers

considered that the neuropathological appearances in one cat were identical with the changes found in the Wernicke syndrome. The mammillary bodies, however, were much less involved than the peri-ventricular area of the hypothalamus.

The age of the animals used in these experiments varied from kittens of six weeks to adult cats; the type of pathological change did not differ in either group. The younger animals, however, were less resistant and died much sooner than the older animals.

Focal lesions with a similar glio-mesodermal proliferation have been produced experimentally in the monkey (*Macaca mulatta*) by Richter (1949). Investigating the effect of certain quinoline compounds, notably substances belonging to the group of 8-amino-quinolines, on the nervous system of the macaque, he found the symptoms and pathological changes so strikingly constant and extreme as to merit a full description. In brief, these changes consisted of a proliferation of capillaries and pre-capillaries within areas of parenchymal destruction. Within the lesion the cell bodies of the neurons, and the interstitial tissue including the oligodendroglia had undergone virtually complete dissolution. The microglia was more resistant and was actively proliferated, both within the core of the lesion and more markedly at the periphery. The selectivity of the focal lesions was remarkable: the thalamus, hypothalamus, red nucleus, substantia nigra, oculo-motor and trochlear nuclei, abducens, vestibular, cochlear, granule and cuneate nuclei, lateral nucleus of medulla, and the reticular formations of the pons and medulla were all affected. Richter concluded that

> "a number of compounds built upon the quinoline nucleus have a peculiarly destructive affinity for the central nervous system depending upon the nature and arrangement of their side chains. In part this toxic action is expressed in relatively selective focal necroses, notably of brain stem nuclei, sensory and motor."

In the subsequent discussion, however, Denny-Brown commented on the "very close resemblance between these lesions and those of Wernicke's encephalopathy" and considered it possible that these substances had an anti-thiamin effect.

Whatever the mechanism, there is no doubt of the very close similarity between these experimental lesions and the findings in the case reported here. Both are fascinating examples of the phenomenon of selective localization in the nervous system. Whether, in this infant, an unknown toxin or virus was responsible for these lesions, or whether the case was primarily a Wernicke's encephalopathy in an infant, is difficult to decide. The clinical history and course do not help greatly in reaching a decision, but are slightly more in favour of a deficiency disorder than an infective or toxic process. Owing to our scant knowledge of early infantile disease processes, it will be an advantage to keep an open mind on the aetiological problem.

Summary

A case is reported of a male infant aged 7 months dying within a period of six weeks from a central nervous system disorder characterized by somnolence, blindness, deafness, and spasticity of the limbs.

The neuropathological findings consisted of focal, bilaterally symmetrical subacute necrotic lesions or softenings extending from the thalamus to the pons, the inferior olives, and the posterior columns of the spinal cord.

Histologically the affected areas showed an intense vascular, microglial and histiocytic proliferation, and a less marked astrocytic increase. There was severe neuronal damage in these areas.

The aetiology and pathogenesis of the condition is discussed.

My thanks are due to Professor H. A. Magnus, of King's College Hospital, who supplied the brain. Professor Alfred Meyer has been a constant stimulus throughout, and I am indebted to Professor Dorothy Russell for her opinion on this case.

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THE USE OF MARCHI STAINING IN THE LATER STAGES OF HUMAN TRACT DEGENERATION

BY

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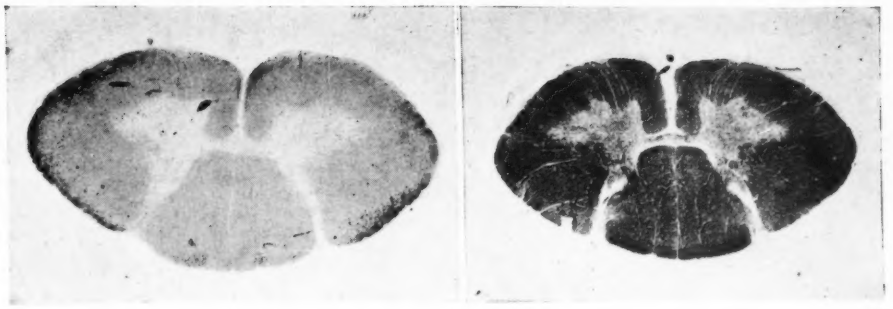
For the purpose of following tract degenerations the Marchi method, or modifications of this method, have been widely used since its introduction in 1885.

Disadvantages in its use include the cost, the fact that the nerve terminals are not displayed, and the various hazards in the preparation of the sections, which are not completely eliminated by any of the modifications used in the staining techniques. Nevertheless the fact that the degenerating myelin of the tracts is stained black, and is thus vividly contrasted against the pale brown of the normal myelin, makes it a most useful method for the easy recognition of even small degenerating tracts.

The method has been applied more to experimental animal work than to human tissue, because it has been thought that positive results could be obtained only after recent lesions. It is the purpose of this paper to show that the Marchi method of staining degenerating fibres is of value in human material even when there is a fairly long interval between the occurrence of the lesion and death. The observations made here relate to the central nervous system in human material, and to direct damage of fibre tracts only ; no deductions have been drawn as to other pathological human material or to animal work.

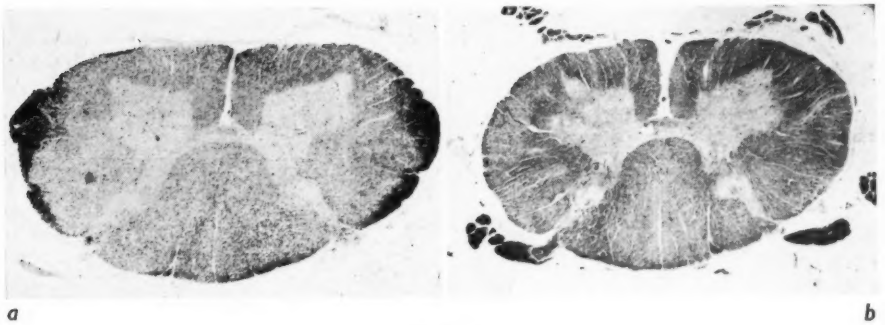
It is clear from the literature that most workers using the Marchi technique have considered it of value only where death followed the lesion within a very short time. In animal work, for example, Allen (1923), working with the guinea-pig, states that " according to my experience with the Marchi method, the maximum degeneration appears in mammals about the eleventh day ". Kingsbury and Johannsen (1927) state that the optimum time will vary, and must often be determined experimentally. Poljak (1933), using Java and Rhesus monkeys, killed his animals 22 to 43 days after the lesion. Swank and Davenport (1934) state that in cats the earliest staining was found at four days, and the maximum at 14 to 20 days. Le Gros Clark (1936), using the Macaque monkey, killed his animals 12 to 14 days after the lesion. Mettler and Hanada (1942) state that in mammals cut myelinated fibres become " osmium susceptible " not earlier than the tenth day, that good results are secured after three weeks, and acceptable sections can be obtained as long as five weeks after the lesion. Strong and Elwyn (1943), with respect to human anatomy, state that the proper stage of degeneration for the use of the Marchi method is one to three weeks after injury. Brodal (1948) states that the changes in degenerating myelin giving rise to the characteristic appearances seen in the Marchi method reach their maximum 14 to 20 days after injury. Glees (1943), however, makes the interesting observation from work on cats and rabbits that Marchi granules could still be seen at the end of one year, although they were then transformed into a very fine, dust-like deposit. He remarks on the probability that the slowness of removal of the degeneration products has not been fully realized, and concludes that this retardation might profitably be used in the study of comparatively long-standing lesions.

Although Hurst (1925), studying the lipoids in neuronic degeneration, obtained staining with osmic acid up to six months after the lesion, and other workers (Kernohan and Woltman, 1929) used this method in lesions of indefinite duration to demonstrate that active degeneration was in process, the value of the Marchi method for tracing degenerating tracts in human material, in which lesions occurred six to 12 months before death, does not seem to have been generally realized. It is probable that observations made regarding the limits of the Marchi



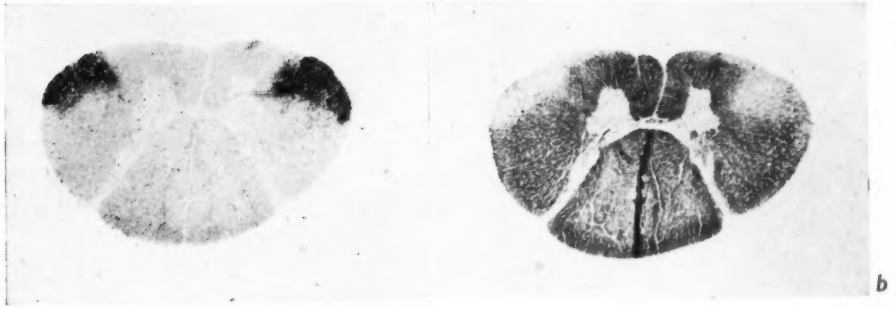
a *b*

CASE 1



a *b*

CASE 2



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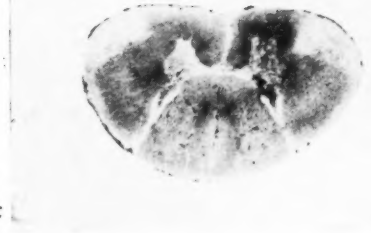
CASE 3



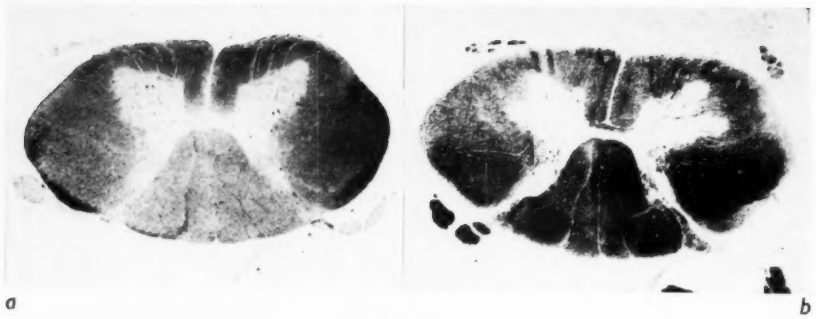
c

All photographs are of sections of spinal cords (× 4½) to show ascending degeneration after spino-thalamic cordotomy.

FIG. 1

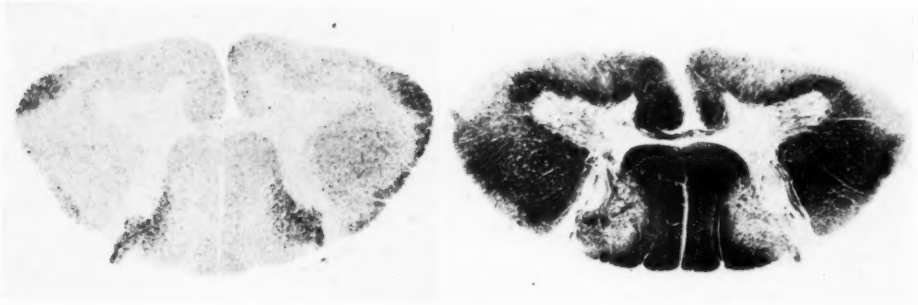
In each case the methods of staining were as follows : Marchi in *a*, Weigert Pal in *b*, except for cases 1*b* and 2*b*, which are stained by Loyez' method. Case 3*c* is stained by Gros' silver method. The sections prepared by the Marchi method show the degenerating fibres stained black. The control preparations (Loyez and Weigert Pal) show the degenerating fibres as pale unstained areas, except in cases 1 and 2 where the interval between operation and death was too short for the degenerating fibres to be shown up by these stains.

The intervals between operation and death were as follows : case 1 : 23 days ; case 2 : 42 days ; case 3 : 123 days ; case 4 : 154 days ; case 5 : 159 days ; case 6 : 313 days ; case 7 : 400 days.



a b

CASE 4

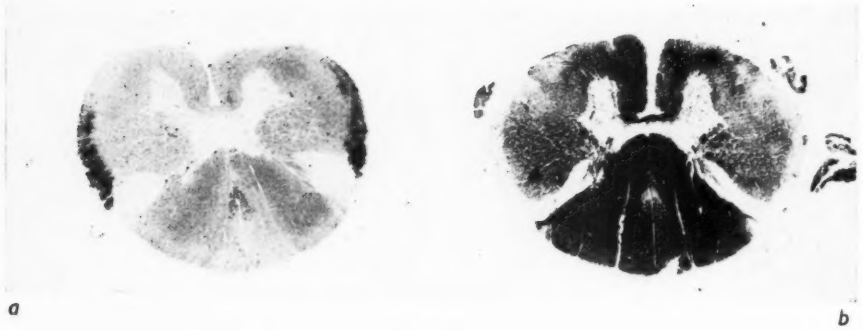


a b

CASE 5

a b

CASE 6



a b

CASE 7

FIG. 2

method have been made on experimental animal material, and applied to human material.

The cases shown here are taken from a series in which the operation of spino-thalamic cordotomy was performed. The interval between the division of the tract, and the death of the patient was therefore known. There was no involvement of the central nervous system before operation.

The method of staining the tissue was the Swank-Davenport technique, modified by Glees (1943); the sections were prepared by the celloidin method. Photographs of these Marchi preparations are shown in Figs. 1 and 2. It is to be noted that they are from sections made as long as four and a half years ago. In fresh sections the contrast between normal and degenerating myelin is more striking. In all cases except case 3 the operation was performed at the mid-thoracic level; sections shown here are from cervical segments, so that degeneration products in tracts at a considerable distance from the lesion may be seen. In case 3, the sections are from the next segment cranial to the lesion. In all the cases, except cases 1 and 2, Weigert Pal preparations from sections adjacent to the area studied by the Marchi technique, have been photographed and are given for comparison (area of degeneration unstained). In cases 1 and 2, Weigert Pal sections were not available, and Loyez' myelin stain preparations have been given in their place. In case 3, a section stained by Gros' silver method is also photographed to demonstrate the similarity of the shape of the degenerated area shown by the three different methods.

The intervals between operation and death are as follows: case 1: 23 days; case 2: 42 days; case 3: 123 days; case 4: 154 days; case 5: 159 days; case 6: 313 days; case 7: 400 days.

The cases shown here illustrate the clear positive Marchi staining present at intervals up to 13 months after the lesion. It is not possible with the longer intervals to be sure that the entire extent of the degeneration is shown in the Marchi preparations, but even at these long intervals a clear indication of the tracts involved is obtainable, and, particularly in the brain, small groups of black degenerating fibres are more easily seen than are the pale areas in a Weigert Pal preparation. The two methods of staining may then be used in conjunction with each other, in topographical investigations in human work, after fairly long intervals.

It seems probable that the optimum time, and the limits of use of the Marchi method, vary in different species. There may well be a different rate of degeneration not only from species to species, but also between different members of the same species, and possibly in different tracts in the same individual. One realizes that there is an optimum period in degeneration when the maximal amount of degenerating myelin stains by the Marchi method. After this period of optimum staining there is likely to be a period lasting some months when staining adequate for tracing tracts can still be obtained.

Summary

Evidence is given showing that Marchi staining is useful in following degenerating nerve tracts in human tissue at intervals up to 13 months after division of the tracts.

My thanks are due to Dr. E. A. Carmichael for his help and criticism, and to Mrs. J. A. Mills for her ungrudging assistance in the technical work and photography.

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NEUROTICISM AND EMOTIONAL INSTABILITY IN HIGH-GRADE MALE DEFECTIVES

BY

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It has been found (O'Connor, 1951) that certain psychological tests provide a means of predicting the amount of emotional instability in high-grade defectives, when the latter quality is rated by psychiatrists acquainted with the patients. The psychological tests were of primary suggestibility, general locomotor coordination, and persistence. The multiple correlation of the results of these tests with emotional instability was 0·463, and they accounted for 21% of the total variance. Neuroticism and instability are terms used by many writers as though they were interchangeable, and the amount of both, when operationally defined, can be measured in part by analysis of the results of psychological tests. The relationship between these two qualities in our sample of high-grade defectives can therefore be studied objectively. How far objective tests, appropriate for distinguishing healthy from neurotic persons of average intelligence, will serve as well to differentiate stable defectives from those defectives who are neurotic or emotionally unstable, can also be investigated.

Accordingly, the data were re-examined to provide answers to the following questions. Is there a relationship between stability-instability and intelligence as measured by tests, in a sample of high-grade defective boys? Can "emotional instability" and "neuroticism" be used as interchangeable terms in describing defectives? Do objective tests which have been found to differentiate normals and neurotics, also detect neurotic defectives, or emotionally unstable defectives, or both? If the two terms are not equivalent, what percentage of defectives can be considered emotionally unstable, and what percentage neurotic?

The Sample and Criterion Rating

The Sample.—This consisted of 104 high-grade defective boys of mean age 20·9 years who were consecutive admissions to the hospital. Most of them were below 20, and only three were more than 30 years old. All were in good health, and free from physical disabilities. The mean of five mean I.Q.s on separate tests was 73·54 with a standard deviation of 16·12 points.

The Criterion Rating.—This was a four point rating of emotional stability-instability, and was made independently by three raters between whom agreement was 0·45, 0·50, and 0·78. After each had rated the members of the sample, disagreements were discussed, and a final rating agreed. The distribution according to the four points of the rating is given in Table I.

TABLE I

ANALYSIS OF PSYCHIATRIC RATING OF INSTABILITY

	N	
Very stable and mature group ..	44	58 = 55·7% stable
Stable but immature group ..	14	
Unstable group	32	46 = 44·3% unstable
Markedly unstable group	14	

Those in the first grade, very stable and mature, were marked by a maturity of judgment, and their social attitude reflected confidence. They showed restraint, and an adult approach to the test interview situations. Those in the second group, stable but immature, were similar, but showed signs of social immaturity, shyness, and uncertainty, The rather unstable group, the third, was noticeably more anxious and preoccupied, or alternatively notably aggressive. They frequently asked questions about themselves and their future, and displayed clear signs of confusion concerning the purpose of the tests used. They appeared suspicious of the tester. Those who were aggressive often had a history of delinquency and truancy, and showed dominance in social group test situations. They seemed generally opposed to authority.

The fourth, or markedly unstable group, were the most difficult to test, and seemed to find concentration an effort. They showed all the symptoms exhibited by the third group in a more marked degree.

Tests

A number of cognitive, motor, and personality tests were given to the sample of 104 defectives. A list of these is given below with a brief description of the less well known tests.

Intelligence Tests.—Kohs blocks (Alexander version); progressive matrices (1938) untimed; vocabulary sub-

test of the 1937 Terman-Merrill revision of the Stanford-Binet test Form L ; Porteus maze (Vineland revision, 1933) ; and Cattell non-verbal intelligence test, Form IB.

Aptitude Tests.—Subtests of the United States Education Service General Aptitude Test were used. (The battery consisted of tests A, C, D, F, G, H, K, L, M, N, O, and P.)

General Locomotor Coordination Test.—The Heath's rail walking test was standardized on an American Army sample of 1,013 infantrymen, and has a reported reliability of 0·94. The test material consists of three rails of wood, two of which are 9 ft. long, and one 6 ft. long. One of the longer rails is 4 in. wide, and the other 2 in. wide. The 6-ft. rail is 1 in. wide. Subjects are asked to walk bare-footed heel to toe along each of the rails three times in succession. Their raw score is the distance in feet they manage to traverse without falling off the rail which is raised a few inches above the floor. Scores are weighted 1, 2, and 4 for the widest, medium, and narrowest rail respectively. The more difficult rails are not attempted by a subject who scores less than eight (raw score) on the preceding rail.

Primary Suggestibility Test.—Hull's body sway test of primary suggestibility was employed.

Persistence Test.—Eysenck's leg test and Fessard's hand dynamometer test were used. In the second persistence test, the subject is asked to press a hand dynamometer until his strength is registered. The movable pointer on the scale is then set at two-thirds of this reading, and the subject is asked to hold the other pointer at this level as long as possible. His score is the number of seconds during which he succeeds in holding the pointer at this mark.

Level of Aspiration Test.—The track tracer test (Cambridge Laboratory) was used.

Results and Discussion

The results are presented and discussed under the headings of the problems considered.

Comparison of Intelligence and Emotional Stability.—Is intelligence as measured by tests correlated with emotional instability ? This question is directly answered by considering the correlation between the matrices test and the criterion rating of stability-instability. This correlation, 0·233, is significant at the 5% level, and indicates a tendency for the emotionally unstable to perform badly on the matrices. Despite the fact that, as a predictor of emotional instability, the matrices test failed in the previous multiple regression study, the correlation must be accepted as established. This result compares with the findings of Dewan (1948) who, while not quoting a correlation coefficient, gives the following figures based on the examination of Canadian soldiers.

The results may be regarded as reliable, because closely similar percentages of instability were recorded for the respective intelligence levels by a number of psychiatrists succeeding each other for duty.*

Evidence on the general question of the relationship between intelligence and emotional instability is conflicting. Weaver (1946), Neuer (1947), and Kingsley and Hyde (1945) hold that among defectives such a correlation exists. Passages in Duncan (1936), Henderson and Gillespie (1941), and Tredgold (1947) also support such a view. Pollock (1944) says " the general rate of incidence of mental illness is higher among subnormal persons than among the general population and our data indicates that the rate of mental disease declines as the degree of intelligence advances ". There is, however, a considerable body of evidence suggesting that cognitive performance is not related to emotional stability or instability. Authors who appear to support this view sometimes quote very low correlations between intelligence test scores and emotional stability-instability measures. Pintner (1945), quoting Hartshorne and May, shows that they found a correlation of only 0·15 between persistence and intelligence. Persistence is regarded by many as a valid test of freedom from neurosis. Eysenck, in a recent discussion of the evidence (1947), notices its conflicting nature, and suggests that differences in findings may be due to sampling. Society may place greater stress on those of more than average intelligence in some circumstances, and greater stress on the subnormal in others. In his own work, he finds a very low correlation between matrices I.Q. (1941 version), and negative personality (— P) or neuroticism. Summarizing his own work, Eysenck holds (1947) that there is likely to be a factor of neuroticism distinct and independent of general intelligence. This is quite consistent with his statement that neurotic soldiers tend to be below average intelligence, providing the explanation of differential social stress, mentioned above, is accepted.

Our own findings and those of Dewan, Pollock, Neuer, Weaver, and others, point to the existence of a higher correlation between instability and I.Q. The first comment to be made about this fact is that these investigations were mostly conducted with defectives, whereas other work has been concerned with those of a higher general level of intelligence. Another point is that the term " emotional instability " may have a different meaning from " neuroticism " as defined operationally by Eysenck. Finally it is possible that stress for the

* It is conceivable that the results are affected by those lower grade recruits who attempt to use psychiatric disability as a means of avoiding military service, but this would probably account for only a part of the difference between low and high grade incidence.

defective of lower I.Q. living in an institution is disproportionately greater than the stress for the higher grade boy.

Definition of Terms.—Can emotional stability-instability and " neuroticism " be used interchangeably in describing defectives? We cannot answer definitively on the basis of our previous investigation because no diagnosis of " neuroticism " was made. However, subsequent work gives a clear indication. Although Tredgold (1947) says that at adolescence it is difficult to distinguish in cases of mental abnormality between high grade defect, psychoneurosis, and dementia; he nevertheless states that hysteria and anxiety neurosis are common among defectives. Defectives are more prone to neurosis than are normals. Penrose (1938), who shares this viewpoint to some extent, notes that hysteria and obsessions, psychopathic personality and depression frequently occur among defectives. In the same paper, Penrose gives figures for the incidence of mild and acute psychopathy, psychoneurosis, and psychosis in 1,280 cases of mental defect. He found 204 cases of psychopathy, 72 of psychosis, and 132 of psychoneurosis. The neurotic cases tended to come from higher mental grades than the average patient examined. The number of neurotic cases represent quite a small percentage of the total, i.e. 9·6%. This is a far lower figure than Dewan's 53·8%. Our own results on a psychiatric rating of instability, based on social behaviour and social competence, are similar to Dewan's (Table II). The 44·3% found

TABLE II

RESULTS OF TEST AND STABILITY-INSTABILITY RATING (DEWAN, 1948)

	Defective	Dull Normal	Normal
Intelligence (M-score)	0–49	50–89	90–119
Instability (%) ..	53·8	39·9	26·7
N	736	2,595	4,695

to be unstable in this investigation includes 12·5% very unstable patients who would certainly be diagnosed as neurotic, but also includes many others. Most of these others, about 30% of the whole sample, do not show clear neurotic signs, and could not be classified as neurotics. Their breakdowns are social failures and cases of indiscipline. Doll (1932) has suggested that although defectives suffer from emotional disturbances, they forget them quickly, and lack the depth of mind to suffer neurosis, and this opinion seems to apply to the cases called emotionally unstable in our investigation. The difference between Penrose's and Dewan's findings might be explained in many ways, but this difference is probably due chiefly to the use of different methods of classification. Our own test findings make it clear, as far as the present sample is concerned, that social incompetence of the high grade defective, often described as emotional instability, must be distinguished from neuroses which have been clinically diagnosed.

Describing the test performance of neurotic soldiers, Eysenck (1947) says that they lack persistence, and tend to be highly suggestible on the Hull body sway test of primary suggestibility. This test was one of the most successful in Eysenck's own battery. Another was the leg test of persistence, and both tests gave comparatively high correlations with psychiatric diagnosis of neuroticism. Our own findings will, therefore, be presented and compared with Eysenck's and those of his associates. The body sway results are presented first. These as well as the persistence scores are also compared with Brady's results obtained on a sample of defective men (1948).

It is clear from an examination of Tables III and IV that defectives as a group do not show a markedly neurotic mean score. This result suggests a need for caution in assuming that defectives as a group contain a high proportion of neurotics.

TABLE III

ANALYSIS OF TEST RESULTS COMPARED WITH THOSE OF EYSENCK (1947) AND BRADY (1948)

Postural Suggestibility		Mean	S.D.	N
Source	Population			
Eysenck	Neurotics	4·18	—*	900
	Normals	1·02	—	60
Brady (1948) ..	Defective males	1·19	0·37	106
This investigation	Defective males	1·30	2·62	104

* Not given.

A similar conclusion must be reached after an examination of the findings of Brady and ourselves for defectives, when these findings are compared with those of Himmelweit, Desai, and Petrie (1946) for normals.

The performance of defectives in this test is clearly different from that of neurotics.

A further analysis of the results shows that whereas the most stable defectives have a lower leg persistence (Table V) than the least stable, the 20 most suggestible have a significantly lower persistence than the 20 least suggestible; " t " was significant at the 5% level. Thus, although these two tests do not select a high proportion of the unstable among defectives, they do show a significant

TABLE IV

POSTURAL SUGGESTIBILITY

Sway (in inches) ..	0	½	1	1½	2	2½	3	3½	4	5	6	7	8	9	12
Eysenck (male) ..	8		18		20		12		10	6	4	3	2	2	16
This investigation ..	34	33	12	10	2	2	3	2				1			5

TABLE V

LEG STABILITY TEST RESULTS COMPARED WITH OTHER AUTHORS'

Persistence			Mean	S.D.	N
The leg test		normals	—	—	—
Petrie (1946, unpublished data)	neurotics	(dysthymics)	29·1	20·8	25
Eysenck (1947)	neurotics	(hysterics) ..	14·16	9·6	25
Brady (1948)		male defective	120·01	20·4	106
This investigation		male defective	69·8	51·04	104

difference between the stable defective and the "neurotic" defective, as defined operationally in Eysenck's terms. On the basis of an operational definition of neurosis in terms of test findings, and recalling the conclusions of Penrose and Dewan, it would seem advisable to use the term "neurotic" more exclusively than the term "emotional instability". Factor analysis of subsequently collected data (to be published) suggests that unstable behaviour is a mild form of neurosis, but on the basis of our findings the two terms appear to have a somewhat different denotation.

Validity of Objective Tests.—Do objective tests, which have been found to differentiate normals and neurotics, detect "neuroticism" or "emotional instability" or both or neither among defectives?

This question has been answered in the course of our consideration of the previous problem. An operational definition in terms of tests, and their cut off points as found effective by previous workers, suggests that only a small proportion, about 12%, of defectives of high grade in an institution such as Darenth Park, can be classed as neurotic. A larger group, about 32%,* without neurotic test scores, can be regarded as emotionally unstable for practical purposes.

Conclusions

The view that I.Q. scores and emotional stability ratings are related among defectives is confirmed by the present test results. A low but significant correlation of 0·233 was found.

The terms "emotional stability-instability" and "neuroticism" or "neurosis" are sometimes considered equivalent when describing defectives. If an operational definition in terms of objective test results is given to "neuroticism", the terms are found to have a different connotation.

Objective tests which were previously found to differentiate normals and neurotics separate a small percentage of defectives from their fellows, but do not reveal a larger percentage of unstable patients unless new cut off points are chosen.

It is suggested that previous findings concerning percentage psychoneurosis (Penrose), and percentage instability (Dewan) are confirmed. In the sample tested, 12% were classifiable as neurotic, and 44% as emotionally unstable.

Summary

One hundred and four high grade adolescent defective boys living in a hospital were tested with cognitive, personality, and motor tests. The tests were used to predict a psychiatric rating of emotional instability. On the basis of an operational definition of "neuroticism" in terms of test findings, the incidence of emotional instability and neuroticism respectively was assessed.

About 43% of the sample are unstable and 12% neurotic. This confirms findings with other samples of defectives (Penrose), and subjects of average intelligence (Dewan). The two terms would not seem to be interchangeable but instability may be a mild form of neurosis. In the sample tested, a low but significant correlation was found between the progressive matrices test and a psychiatric rating of emotional instability.

* Eysenck has recently advanced a theory of neuroticism which suggests that a continuous scale of neurotic predisposition exists (unpublished paper). Our own findings support this view. The 32% emotionally unstable may be mildly neurotic.

The work was carried out, in the course of investigations by the Occupational Psychiatry Research Unit of the Medical Research Council, by J. Tizard and the author. Patients were tested at Darenth Park, Dartford, and the author wishes to acknowledge the very considerable assistance which the Physician Superintendent, Dr. J. K. Collier Laing, has given to the investigators. We also wish to thank Dr. J. M. Crawford for the help which he gave in selecting patients and assisting with the criterion ratings.

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BOOK REVIEWS

Fainting : Physiological and Psychological Considerations. By George L. Engel. 1950. Oxford : Blackwell Scientific Publications, Ltd. ; Springfield, Illinois, U.S.A. : Charles C. Thomas. 1st ed. Illustrated. Pp. 140. Price 20*s*.

This small volume contains a short account of the different clinical syndromes and mechanisms comprised under the head of fainting. It is valuable, because it covers ground of equal interest to the neurologist, psychiatrist, cardiologist, and general physician, but ground known to each much better in some parts than in others. Here in simple form is a map of the whole, with selected references to recent literature. It is comprehensive and generally well balanced, but there is a tendency, difficult to avoid in such a short work, to oversimplification. The reader may accept the view that in young persons, especially women, fainting is more often than not hysterical, provided he appreciates that, in the author's definition, a faint does not require loss of consciousness as an essential feature. The reader may, on the other hand, be unwilling to agree with the notion apparently emerging from this book, that all attacks, not fitting into any other classification, must therefore be labelled as hysterical. The author's qualification that the hysterical faint must be capable of symbolic interpretation, is no safeguard against the danger of dismissing a syndrome from further consideration, merely because it is, at present, not understood, because anyone with a little imagination can devise symbols by the dozen.

In the chapter on differential diagnosis, the epileptic variants, especially those with visceral symptoms, are inadequately discussed, and the neurologist may also disagree with the statement that myoclonic epilepsy is that form of epilepsy in which the patient has a sudden loss of muscle tone and falls to the ground, and that familial periodic paralysis is characterized by a weakness which develops so rapidly that the patient falls to the ground completely paralysed. Such statements cause one to consider with reserve the author's opinions about fainting in less familiar fields, such as the cardiological. The distinction between hysterical attacks and psychogenic faints is clearly made, but when the author expresses uncertainty as to whether psychological factors may lead to a sufficient increase of vagal tone to cause asystole and syncope, he underestimates the evidence to the contrary.

These, however, are minor blemishes in a work which contains much valuable information not easily available from other sources. It is clearly written and easy to read, and should be studied with profit by all practising neurologists.

The Neurologic Examination. Incorporating the Fundamentals of Neuroanatomy and Neurophysiology. By R. N. DeJong. 1950. London : Cassell and Company. Pp. 1079, with 368 illustrations. Price 110*s*.

This large work clearly sets out to be a comprehensive text on the examination of the nervous system. The difficulty with any such attempt is that it is bound to include much that is so elementary as to be almost unnecessary, and to miss out something which any given neurologist's own clinical experience leads him to consider important. Further, if inclusiveness is to be balanced by criticism, the text becomes impracticably lengthy. This book has avoided the first two difficulties in some measure, though considering its size, adjuvant methods such as intracranial air studies, angiograms, etc., get scant attention ; but there is a tendency to include quoted facts without any counterbalancing critical evaluation. References to neuroanatomy and physiology are up to date and useful. The index is occasionally inaccurate. In general it may be doubted whether works of this sort now have much place in neurological literature.

Erkrankungen des Nervensystems. By Fritz Roeder. 1950. Göttingen : Musterschmidt. 140 text figures. Pp. 612. Price DM. 32.–

This is an uninspiring book. It is presumably intended as a standard textbook of post-war German neurology for the use of senior students. It illustrates the disadvantages of wars and isolation to the general standard of clinical knowledge, for the references in each section are mainly to German literature, and most of the non-German references mentioned are already out of date. The book therefore reads as though it had been written a decade ago. To some extent most textbooks give this impression, but in the first edition of a new work it is usually avoided. The general lay-out is anatomical. After introductory sections on anatomy, physiology and the cerebo-spinal fluid with brief mention of electrical methods of diagnosis, peripheral and cranial nerve diseases (including the peripheral element of the autonomic system), are discussed. The myopathies and spinal cord disease lead on to cerebral syndromes. Finally, the anatomical approach is abandoned, and infections (including syphilis), congenital and degenerative diseases, the extrapyramidal syndromes and toxic and deficiency conditions are considered. A separate chapter is devoted to convulsive disorders. Recent advances in drug treatment both in infections and convulsive disorders are inadequately mentioned, if at all.

The book is well produced and has a good index.

Modern Trends in Neurology. Edited by Anthony Feiling. 1951. London: Butterworth & Co. 202 plates; Pp. 717. Price 63*s*.

This rather expensive volume contains 20 articles by different authors on current neurological and neurosurgical topics. Most of these provide excellent accounts of current knowledge on subjects such as the conduction of the nervous impulse, the frontal lobes, headache, cerebral palsies of infancy, arachnoiditis, meningitis, poliomyelitis, radiculitis and syphilis of the nervous system. The editor expresses the belief that "neurologists will find this book a valuable and even indispensable addition to their library". For those who keep in touch with neurological literature, some of these chapters will have little appeal, but all should find some chapters of interest.

Die Differentialdiagnose der Gehirngeschwülste durch die Arteriographie. By Mario Milletti. 1951. Acta Neurochirurgica, Supplementum 1. Vienna: Springer-Verlag. With 64 radiographs and 3 text figures. Pp. 79. Price £2.

This monograph is based on a study of 203 cases of brain tumour examined by means of arteriography. In the first part, a review is given of the relevant literature. This is followed by a description of the angiographic characteristics of various brain tumours, in which the opinions of many writers are quoted. The author's own observations are summarized in the third part of the paper, and his conclusions conform in most cases to those which are generally accepted.

A pathological circulation was observed in 104 of the 203 cases studied. In the so-called negative group in which this was absent, the majority of lesions were benign. The primary concern of the author was to distinguish benign from malignant tumours, and secondarily he differentiated them into types. How far he has succeeded in the former may be judged by the fact that a misdiagnosis of malignancy in a benign tumour was made in only four of the 104 cases in which a pathological circulation was visible. No malignant tumours in this group were thought to be benign. The distinction cannot, however, be made with certainty in the "negative" cases. The difficulties of distinguishing different types of malignant tumour are emphasized. Sixty-four arteriograms are reproduced.

It would be interesting to know more details of the histological criteria on which the diagnoses were based. This applies particularly to the sarcoma group (six cases), for such diagnosis is seldom made in this country. It would also be of interest to know the histology of the whole tumour in those astrocytomas in which a pathological circulation was seen (two cases), because parts of these might possibly have been undergoing a process of malignant change.

The problem of the differentiation of brain tumours by means of angiography will probably not be solved until more factors are taken into account than the appearances of the arterial phase alone. The circulation time and the nature of the venous vascular channels are particularly important, and also the correlation of vascular patterns with anatomical data. Although the author has stressed the need for a complete study of the progress of contrast through the cerebral circulation, phlebograms were not made in any of his cases: this monograph, therefore, inevitably lacks a sufficient emphasis on these aspects. It will nevertheless be found to contain a useful record of present day knowledge of the subject.

Hirnverletzungen. By W. Birkmayer. 1951. Vienna: Springer-Verlag. 54 illustrations. Pp. 292. Price 51*s*. 6*d*.

This book is based on the experience of cases of head injury in Vienna during and after the last war. Its author is an assistant in Professor Pötzl's neuropsychiatric clinic, and was neurologist to the special hospital for brain injuries.

After an opening discussion on the mechanism of brain injury in both penetrating and "blunt" head injuries, late complications of brain wounds such as meningitis, abscess, and epilepsy are reviewed. Management and treatment are considered with very little reference to modern chemotherapy. The only anticonvulsants mentioned in any detail are the barbiturates: though boric acid is apparently still being used by the author. These sections are therefore of little value. Motor disabilities are next considered, and a fairly full description of their retraining and physiotherapy is given. A chapter is devoted to lesions of autonomic functions: here the biochemical findings are interesting, but correlation with anatomical brain lesions is inadequate. Further chapters on intellectual disabilities and sensory changes including body schema and spatial disorientation are included. In these, the site of lesion is considered in more detail, though information on this point is still rather meagre—broad groupings such as frontal, parietal, etc., are used without further definition; except for the group showing spatial disorientation and visual disturbance, where site of wounding is plotted on a schematic diagram showing the outline of skull and brain. Disorientation is far commoner with right sided wounds, though the number of such wounds showing hemianopia *without* disorientation seems surprisingly small. In general, the book does not add much to knowledge of brain localization, though occasional case histories are of interest. As a serious reference book it is greatly handicapped by having no index. Further, it is curiously lacking in references to English and American work, either in the relevant fields of neurophysiology and anatomy, or in the more direct clinical sphere. This creates the impression that it is based on the problems and the state of knowledge of twenty years ago. Professor Pötzl, in an introduction, mentions Kleist's "Hirnpathologie" of the 1914–18 war, but the present book falls far short of Kleist's considerable *Arbeit*. The book costs an exorbitant price as most German publications do at present.

Skull Fractures and Brain Injuries. By H. E. Mock. 1950. London: Baillière, Tindall and Cox; Baltimore: Williams & Wilkins Company. Pp. xiv + 806 with 116 figures. Price 114*s*.

The author of this expensive book begins by explaining

why he, as a general surgeon, has written it. Clearly he has a wide experience of treating accidental cases of head injury, but it can hardly be said that his study provides much advance in knowledge.

Much of the discussion is uncritical, and includes a jumbled collection of quotations from other authors, which are often frankly misleading. Many important aspects of the subject are simply not considered, while his views on subjects such as the importance of dehydration are based on statistics which few will accept. He advises conservative treatment for cerebrospinal rhinorrhoea, and even for traumatic pneumatocele, suggestions which will shock most neurosurgeons. There is a comprehensive index in which this reviewer has sought in vain for information about the treatment of meningitis, the effect of crushing injuries, the early recognition of injuries to optic nerve and chiasm, traumatic decerebrate rigidity, prognosis in traumatic diabetes insipidus, treatment of delayed intracranial haemorrhage. Indeed the index is curiously unhelpful ; under meningitis, for example, there are several entries but none refers to treatment.

Électroencéphalographie et Électrocorticographie de l'Épilepsie. Published by H. Fischgold. Paris : L' Expansion Scientifique Française. 127 text figures. Pp. 140. Price Fr. Fr. 1.600.–

The proceedings of the second International Congress of Electroencephalography held in Paris in 1949, published in this volume, represent a useful symposium on the sort of problems (theoretical as well as practical) that occupy the attention of those working in this field. Formal papers and the reports of more informal discussions are both included. The list of contents shown below gives an indication of the range of subjects treated. It should provide something of interest for those practising in all branches of neurology.

I. *Rapports*
W. Grey Walter (Bristol). "The Principles and Methods of Location."
H. Jasper (Montréal). "Electrocorticograms in Man."
A. Earl Walker. "Electrocorticography in Epilepsy : A Surgeon's Appraisal."
M. Brazier (Boston). "A Study of the Electrical Fields at the Surface of the Head."
W. S. McCulloch (Chicago). "*Signes électriques des évènements 'à distance' dans le système nerveux central.*"
V. J. Walter et W. Grey Walter (Bristol). "The Effect of Physical Stimuli on the E.E.G."
H. Gastaut (Marseille). "*Effets des stimulations physiques sur l'E.E.G. de l'homme.*"
A. Remond (Paris), C. Dreyfus-Brisac (Paris), et Y. Laporte (Toulouse). "*Effet des activations chimiques sur l'électro-encéphalogramme humain.*"

II. *Conferences*
H. Jasper (Montréal). "*Étude anatomo-physiologiques des épilepsies.*"
W. C. McCulloch (Chicago). "*Comment les structures nerveuses ont des idées.*"

III. *Symposium sur la classificatlon des épilepsies*
H. Jasper et John Kershman (Montréal). "Classification of the E.E.G. in Epilepsy."

Atlas of Electroencephalography. By F. A. Gibbs and E. L. Gibbs. 1950. Massachusetts : Addison-Wesley Press. Vol. I. 2nd Ed. Illustrated. Pp. 324. Price $17.50.

The Gibbs' atlas of electroencephalography was first published in 1941. It has since become the standard reference work on this subject, and indeed, until quite recently, the only comprehensive textbook on the clinical aspects of the electrical activity of the brain. Now, in the second edition, it has been expanded into two volumes, the first of which, reviewed here, is concerned only with methods and controls. It is significant of the growth of the subject, that, already, the first part is nearly a hundred pages longer than the first edition of the whole work. The section on theoretical background has been enlarged, and now forms an adequate introduction to further reading. Various new techniques of electrode placement and recording are described. The main part of the book is, however, made up of well reproduced EEG tracings (arranged as before according to age groups) illustrating normal records and artefacts, with explanatory comments. It is axiomatic in clinical work that as experience grows, concepts of the range of normal variations become wider, and definition of the pathological becomes more precise. This process, helped by refinements in technique, has been occurring in EEG work during the past decade : so that this record of the range of normals drawn from the authors' vast clinical material, is invaluable. The book is well indexed, and contains a full range of references, both to classical papers and to recent work. In the introduction, there is a brief biographical note on Hans Berger, the remarkable founder of clinical electroencephalography. If the second volume maintains the high standards of the first, this work, despite its size, will remain an indispensable vade mecum to all those concerned with electroencephalography.

Psychologische Untersuchungen über Bewusstseinsveränderungen in der Insulinkur. By G. Pflugfelder. 1951. Basle : S. Karger. Illustrated. Pp. 78.

As a result of the application of standardized mental tests throughout the various stages of insulin shock treatment, the author has some interesting things to say about the pattern of regression in declining consciousness, and about some of the accepted psycho-physical typologies. Great emphasis is placed, however, on the difference between hypoglycaemic coma and loss of consciousness from other causes, so that there are regrettably few conclusions of general interest and wider significance.

Although the attempt to make use of the experimental opportunities afforded by modern physical methods of treatment is a welcome one, it is doubtful whether the use of popular tests is necessarily valuable in this field. More information about the mental functions affected is derived from the author's description of performance on tests devised by himself to verify clinical observations, than from the application of standardized measurements of perception or intellect.

Recent Progress in Psychiatry. Edited by G. W. T. H. Fleming. 1950. London : J. & A. Churchill Ltd. Journal of Mental Science, vol. 2. Pp. 711. Price 50*s*.

This book will be of considerable interest to neurologists and general physicians as well as to psychiatrists.

Each article makes some attempt to review the literature of its subject for the years after 1943. All contain much quoted information, though they differ in the degree to which this is critically surveyed. This is conditioned to some extent by the material reviewed, but also by the experience and maturity of the writer. In this respect Professor Golla's article on physiological psychology seems especially valuable in presenting and evaluating recent findings. The neuropathology of oligophrenia, Dr. R. M. Norman's contribution, is also a most useful review of a subject to which growing attention is again being paid. Cybernetics has evidently fired the imagination of many psychiatrists, and apart from Dr. W. Ross Ashby's contribution with this title, its methods and concepts are referred to in several of the other articles. The enthusiasm is not, perhaps, as great now as when these articles were written a year or so ago, and it is still too early to judge whether Dr. Ashby's hope, that the techniques of cybernetics may provide a new era of psychiatric advance, will be fulfilled.

The range of subjects is wide, and includes psychiatric genetics, electroencephalography, biochemistry, endocrines, neuropathology, neurosurgery, senescence, aspects of schizophrenia and mental testing.

Many of the articles are concerned with the borderlands of psychiatry—neurology, physiology, biochemistry, and so on. Indeed this volume reflects an atmosphere that seems prevalent in psychiatry at the moment, when there are many " growing points " at the periphery, but somehow less at the central core of the subject. This may not be a bad phase of growth and development, and is perhaps inevitable in an intellectual climate where philosophers and psychologists prefer their psychology without a " psyche ".

Réflexions sur la Psychoanalyse (Collection " L'Education Familiale nouvelle "). By J. Lhermitte, J. Boutonier, M. Nédoncelle, Verine. Paris : Bloud & Gay. Pp. 192. Price Fr. fr. 225.–

This book would seem to be part of a movement that is agitating Catholic countries at present—a movement to reaffirm for intellectuals the authority of the Church in the sphere of morals and human behaviour. Dialectical materialism, psychoanalysis, existentialism and the modern positivists have all either explicitly or implicitly attacked the Church's position, some with more success than others. Now, so it seems to the non-Catholic onlooker, the Church is girding its loins afresh for counter attack. In this book the implications of psychoanalysis in the spheres of education, religion and morals are criticized, sometimes acutely. Although some of the authors are well known in medicine, their criticism is based more on logical and philosophical than on medical grounds. It is important to emphasize this outlook, otherwise the book might acquire a spurious authority. The arguments are not new. They are largely those that were first brought against psychoanalysis and are perennially in action against any apparent materialism. This does not mean they are invaild : but it tends to make the book's exemplification of one of the intellectual trends of our times, rather than any intrinsic merit in its arguments, its main interest for the general reader.

Le Cerveau et la Pensée. By Jean Lhermitte. 1951. Paris : Bloud & Gay. Pp. 208. Price Fr. Fr. 320.–

A concern for the philosophical implications of neurology is perhaps more prevalent on the Continent than in this country. None the less, no neurologist can fail to be interested in Professor Lhermitte's mature reflections on cerebral physiology, consciousness and memory, and the problem of functional localization in general. Broadly, his aim is to survey recent facts and theories in neurology of relevance to the mind-body problem. His information, simply presented for the general reader, is both pertinent and topical. Thus both hemispherectomy and " le feedback " are mentioned. The general argument is developed with persuasion and wit, and this little book will assuredly find its place in the distinguished French tradition of scientific humanism.

It is impossible to deny that Professor Lhermitte's conclusions will be somewhat of a disappointment to those of us who look to neurology for a better understanding of matters psychological. Arguing from the standpoint of a rigid cartesian dualism, the author holds out little hope that consciousness, intelligence, or memory will ever be related in any fundamental way to nervous structure and function. The search for a cortical localization of psychological functions he dismisses as the pursuit of a chimera. Although neurology may prove relevant to the study of some aspects of behaviour, it can never, in Professor Lhermitte's view, elucidate the fundamental problems of mental life. These, it is implied, will continue to exercise man's wit at the level of philosophical disputation.

This little book must not be confused with a work of identical title published by Professor Henri Piéron some 25 years ago. To avoid repetition, it might seem a pity that Professor Lhermitte did not see fit to entitle the present volume *L'Image de Notre Ame*.

Pavlov : A Biography. By B. P. Babkin. 1951. London : Victor Gollancz Ltd. Pp. 364. Price 25*s*.

The first half of this book is a personal biography of Pavlov. Written by the late Professor Babkin, who was a student and colleague of Pavlov's in the early part of the century, it is a sympathetic and fascinating vignette of this great man. At the present time, any picture of Russian life that deals with the more fundamental emotional and temperamental aspects of the Russian character has a special interest. Here we have an obviously authentic picture of the life of a man of science in a land where the old Imperialist régime was breaking up, and the new and more straitening orthodoxy was not yet firmly established. The attitudes and personal relationships described in this biography have a flavour that is strange to Westerners, and which, one must admit, despite a recent overemphasis of the comparison, is reminiscent of the characters in the works of Turgenev and Dostoevski. Nevertheless there clearly emerges the portrait of a man who was devoted to the high ideals of service to scientific truth and thus to the betterment of humanity, a man who at times combined this idealism with an engaging simplicity in worldly affairs.

Pavlov's conception of " nervism ", in which all the

activities of the body are considered to some extent as controlled by the central nervous system, was undoubtedly influenced by the views of Botkins, one of his earliest chiefs; and this conception presumably influences Speranski and his followers in our own day.

Sechenov's "Reflexes of the Brain" was probably the main source of Pavlov's first interest in conditioned reflexes as a method of approaching behaviour and "psychic" activity. These questions are fully discussed in the biography, but the reference to Bechterov, whose contributions to neurophysiology remain important, is perhaps unduly scathing, and this is understandable, because Dr. Babkin knew Bechterov personally as an unsatisfactory guide to scientific endeavour before Babkin came under Pavlov's influence.

In the second half of the book the three main aspects of Pavlov's physiological contributions—regulation of the circulation, the work of the digestive glands, and conditioned reflexes—are considered in more detail. The range and depth of Pavlov's enquiries are impressive.

This book should be widely read by all those interested in the fundamentals of biological science. It also has special merit as the work of a liberal scientist who has seriously considered the position of science in culture, and is writing of the man who obviously moulded his own thought deeply; both men were also indelibly Russian.

A Study of Epilepsy in its Clinical, Social, and Genetic Aspects. By C. H. Alström. 1950. Copenhagen: Munksgaard. Pp. 284. No price stated.

This supplement to the *Acta Psychiatrica et Neurologica* maintains its usual high standard of typography and general layout. It is based on the study of 897 cases of epilepsy seen in neurological practice in Stockholm. Earlier chapters deal briefly with types of attack, prognosis and treatment, and cases are grouped aetiologically under the three headings "cause unknown", "probably known", and "certainly known". The author makes a special plea for this classification rather than that of idiopathic and symptomatic, though it is doubtful whether he makes a very strong case. As far as mental changes and the epileptic personality are concerned, he finds that such traits are common among those cases we would call "symptomatic", and especially in post-traumatic cases. He remarks here that the attempt to force the psychopathological symptoms into a few types of personality is a failure; "the application of elaborate clichés to a large number of patients is a violation of the actual facts"—and many specialists working with epileptics would agree with this statement. In a chapter on social aspects, the view of epileptic criminality is largely discounted. The chapter on genetic factors is a long and important one. His figures seem to suggest that in Sweden, at any rate, the incidence of epilepsy in relatives of epileptics is no larger than it is among the general population, and the family histories of oliogophrenia and psychoses seem also to be no greater. The Swedish laws forbidding marriage to epileptics of "constitutional" type are reviewed and criticized. This book is certainly worth the attention of all those working on epilepsy.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

50,000 Outside the Law. An Examination of the Treatment of those Certified as Mental Defectives. London: The National Council for Civil Liberties. 1951. Pp. 40. Price 1*s.* 3*d.*

* **A Study of Epilepsy in its Clinical, Social, and Genetic Aspects.** By C. H. Alström. 1950. Copenhagen: Munksgaard. Pp. 284. No price stated.

Die Moderne Psychiatrische Schockbehandlung. By Walter Ritter von Baeyer. Stuttgart: Georg Thieme. Pp. 161. Price DM. 14.40 ($3·45).

Clinical Uses of Intravenous Procaine. By David J. Graubard and Milton C. Peterson, edited by William W. Mushin. 1951. Oxford: Blackwell Scientific Publications. Illustrated. Pp. 84. Price 8*s.* 6*d.*

Scientific Thought in the Twentieth Century. Edited by Prof. A. E. Heath. London: Watts & Co. Ltd. Pp. 387. Price 42*s.*

Spezielle Pathologie der Krankheiten des Zentralen und Peripheren Nervensystems. By Gerd Peters. 1951. Stuttgart: Georg Thieme. 214 text figures. Pp. 437. Price DM. 56·–.

* **Électroencéphalographie et Électrocorticographie de l'Épilepsie.** Published by H. Fischgold. 1951. Paris: L'Expansion Scientifique Française. 127 text figures. Pp. 140. Price Fr. Frs. 1,600·–.

Le Syndrome d'Induction Sensorimotrice dans les Troubles de l'Equilibre. Contributions à l'Etude des Relations entre les Troubles Kinétiques et Sensoriels dans les Atteintes Frontales ou Cérébelleuses. By L. Halpern. 1951. Paris: Masson & Cie. 33 text figures. Pp. 106. Price Fr. Frs. 400·–.

Schizophrenic Art: Its Meaning in Psychotherapy. By Margaret Naumburg. 1951. London: William Heinemann Medical Books Ltd. Illustrated. Pp. 247. Price 70*s.*

Studies in Lobotomy. Edited by Milton Greenblatt, Robert Arnot, and Harry C. Solomon. London: William Heinemann Medical Books Ltd. Illustrated. Pp. 495. Price 63*s.*

The Abnormal Pneumoencephalogram. By Leo M. Davidoff and Bernard S. Epstein. 1950. London: Henry Kimpton. 695 illustrations on 289 figures. Pp. 506. Price 105*s.*

* **Le Cerveau et la Pensée.** By Jean Lhermitte. 1951. Paris: Bloud & Gay. Pp. 208. Price Fr. Frs. 320·–.

* Reviewed in this issue.

Emotions and Clinical Medicine. By Stanley Cobb, with an Introduction on Semantics and Definitions by J. R. Reid. 1950. London : Chapman & Hall. Pp. 243. Price 15*s*.

* **Skull Fractures and Brain Injuries.** By Harry E. Mock. 1950. London : Baillière, Tindall and Cox ; Baltimore, U.S.A. : The Williams & Wilkins Company. 116 text figures. Pp. 806. Price 112*s*. 6*d*.

* **Psychologische Untersuchungen über Bewusstseinsveränderungen in der Insulinkur.** By G. Pflugfelder. 1951. Basle : S. Karger. Illustrated. Pp. 78.

The Normal Encephalogram. By Leo M. Davidoff and Cornelius G. Dyke. 1951. London : Henry Kimpton. 3rd ed. 156 text figures. Pp. 240. Price 42*s*.

Theory of Mental Tests. By Harold Gulliksen. 1950. London : Chapman & Hall ; New York : John Wiley & Sons, Inc. Pp. 486. Price 48*s*. ($6·00).

* **Réflexions sur la Psychanalyse** (in the collection "L'Education Familiale nouvelle"). By J. Lhermitte, Juliette Boutonier, M. Nédoncelle, Verine. 1951. Paris : Bloud & Gay. Pp. 192. Price Fr. Frs. 225·–.

The Electrical Activity of the Nervous System. (A textbook for students.) By Mary A. B. Brasier. 1951. London : Sir Isaac Pitman & Sons. 96 text figures. Pp. 220. Price 25*s*.

* Reviewed in this issue.

Symbolic Realization : A New Method of Psychotherapy Applied to a Case of Schizophrenia. By M. A. Sechehaye. 1951. London : Bailey Bros. & Swinfen Ltd. ; New York : International Universities Press, Inc. Monograph Series on Schizophrenia No. 2. Pp. 184. Price $3·25.

More About Psychiatry. By Carl Binger. 1951. London : George Allen & Unwin. Pp. 201. Price 10*s*. 6*d*.

Medical Neuropathology. By I. Mark Scheinker. 1951. Oxford : Blackwell Scientific Publications ; Springfield, Illinois : Charles Thomas. 186 text figures. Pp. 372. Price 75*s*.

Lehrbuch der analytischen Psychotherapie. By Harald Schultz-Hencke. 1951. Stuttgart : Georg Thieme. Pp. 332. Price DM. 27·–.

Grundriss der traumatischen peripheren Nervenschädigungen. By G. Bodechtel, K. Krautzun, and F. Kazmeier. 1951. Stuttgart : Georg Thieme. 78 text figures. Pp. 106. Price DM. 10·20.

Hirnatrophische Prozesse im mittleren Lebensalter und ihre psychischen Erscheinungsbilder. Friederich Wilhelm Bronisch. 1951. Stuttgart : Georg Thieme. 43 text figures. Pp. 105. Price DM. 12·60.

An Introduction to Modern Psychology. By O. L. Zangwill. 1950. New York : The Philosophical Library, Inc. 20 diagrams. Pp. 220. Price $3·75.

THE MAY (1951) ISSUE

The May (1951) issue contains the following papers :

Subacute Cortical Cerebellar Degeneration and its Relation to Carcinoma. By W. Russell Brain, Peter M. Daniel, and J. Godwin Greenfield.

Ischaemic Lesions of Peripheral Nerves : A Review. By R. L. Richards.

Repetitive Discharges in Human Motor Nerve Fibres During the Post-Ischaemic State. By Eric Kugelberg and William Cobb.

Neuromuscular Disorders Amenable to Wheat Germ Oil Therapy. By Reuben Rabinovitch, William C. Gibson, and Donald McEachern.

The Clinical Features and Response to Cortisone of Menopausal Muscular Dystrophy. By G. Milton Shy and Donald McEachern.

The Surgical Treatment of Extrapyramidal Diseases. By Paul C. Bucy.

Disabilities and Progress in a Dysphasic University Student. By M. B. Elvin and R. C. Oldfield.

A Case of Gustatory Sweating. By H. I. Tankel.

Spinal Meningitis Due to *Actinomyces Bovis* Treated with Penicillin and Streptomycin. By Colin Edwards, W. A. Elliott, and Keith J. Randall.

Electrical Activity of the Human Brain During Artificial Sleep. Part 2. Regional Differentiation of Response to Barbiturate Sedation. By B. D. Wyke.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 7s. 6d.

J. Neurol. Neurosurg. Psychiat., 1951, **14**, 237.

HEREDITARY SENSORY RADICULAR NEUROPATHY

BY

D. DENNY-BROWN

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In 1922 Hicks gave a clinical description of a remarkable family of 34 members spread over four generations, 10 of whom suffered from " perforating ulcers of the feet, shooting pains about the body, and deafness ". He remarked that " the condition is very nearly similar in all the patients, so that it is easy to describe a common type of the disease ". He noted an onset with a painless corn in the great toe, giving way to an ulcer with indurated edges and purulent discharge after a few months. Under treatment the ulcer healed, but soon broke down again, and this intermittent healing and relapse then continued for the rest of the life of the patient. The process affected other toes, bone became exposed, and pieces of sequestrum were discharged. Finally there was considerable deformity. After an interval varying from a few months to several years shooting pains began to attack first the lower limbs, then the shoulders, head, or any part of the body. Each pain was very brief and the pains had been frequently diagnosed as lightning pains. About the time of onset of the pains the patient began to suffer from bilateral, slowly progressive deafness, leading eventually to complete loss of hearing. Hicks found that the reflexes of the lower limbs were lost, first the ankle jerks, then the knee jerks, and he had never been able to elicit a plantar response. The reflexes in the upper limbs were retained, as also were the abdominals. The pupils always reacted to light and to accommodation. Apart from the loss of hearing there was no other evidence of impaired function of the cranial nerves. Nystagmus was not present.

Sensation in the upper limbs was unaffected, but in the feet and legs it was severely impaired. Tactile sensation was lost over the first toe and interdigital cleft. Sensation to pain, heat, and cold was lost over a larger area extending to the rest of the foot, or even over the leg. In two cases there was very slight weakness of movements of the foot, more in a third. The Wassermann reaction of the blood was negative in two cases, and in one it was first doubtful and later negative. Death had occurred at the ages of 51, 46, 46, and 49 from causes not directly related to the ulceration. Hicks gives details of 22 cases substantiating this general account.

This remarkable disease, with its marked resemblance to tabes dorsalis, has been assumed to be a great rarity, and the absence of reports of pathological examination or even of the cerebrospinal fluid in any of Hicks's cases added some possible doubt as to the nervous pathology. Hereditary and familial perforating ulcers of the feet had previously been reported by Bruns (1903), Schultze (1917), and by Göbell and Runge (1914). Bruns described a family of five siblings, the four younger members of which suffered from perforating ulcers of the feet appearing first at the age of 17. Schultze described a family of three, a brother and two sisters, who suffered from perforating ulcers of the feet, with loss of knee and ankle jerks and of sensation in the feet. He considered lumbo-sacral syringomyelia the probable cause. Göbell and Runge (1914) had described a family in which nine members in two generations had suffered from similar ulceration. Two members were observed, and in these the knee jerks were retained, and loss of sensation was doubtful. In none of the cases described by those other authors is there mention of deafness or of shooting pains. Syringomyelia, tabes dorsalis, polyneuritis, and leprosy are discussed as possible causes. Predominant loss of sensation to pain and temperature leads all authors to incline to the first of these. Hicks considered that the condition " bears some resemblance to syringomyelia ". Guillain and Thévenard (1929) have since reported two brothers suffering from perforating ulcers of the feet, with dissociated sensory loss up to the knee, but without deafness or shooting pains, under the title " familial syringomyelia ". This report and others will be further discussed below.

Personal Case

Our interest in the condition was aroused by an opportunity to examine Miss R., a woman of 54 years of age, admitted to the National Hospital,

Queen Square, London, under the care of Dr. F. M. R. Walshe in April, 1936. She was a member of the third generation of the family described by Hicks (No. 10 on his table, see Fig. 1). By 1936 many of the affected members of the first and second generations had died. Three out of six in the second generation and eight out of 22 in the third generation were affected. There are at least seven members of the fourth generation, one of whom was probably affected. The fully affected members numbered four males and six females, and transmission of the disease had occurred by both sexes (Fig. 1). The age of onset had been usually between the 22nd and 36th year of life, though one member is said to have suffered from the age of 15 years. A summary of the status of the family, at the time of our examination in 1936, containing data kindly provided by Dr. M. J. McArdle, is presented as the appendix. Denny-Brown and McArdle reported the findings in this case at a meeting of the Association of British Neurologists in 1937. The published report has been delayed in the hope that Dr. McArdle could make a clinical survey of the whole family. This, however, has not yet been possible, and my conclusions remain as they were in 1937.

The patient, Miss R., had been a seamstress, employing five or six girls, until the age of 38 when she had to give up her work on account of the trouble with her feet. For eight years she had been unable to do any needlework on account of difficulty in using her fingers.

About the age of 22 years the patient first noticed a small black area on the ball of the right great toe. There was no apparent cause. After some weeks an ulcer formed, and took about a year to heal. The next ulcer appeared when she was about 30 years of age, and ever since that time she had suffered from recurrent ulceration under the toes and the ball of the foot. The dorsum of the foot and the heel had never been affected.

Each ulcer lasted six to nine months and on occasion extended down to bone, and pieces of bone had been extruded. She had occasionally been free from ulceration for as long as a year. The ulcers occasionally ached when she rested in bed, and especially at night, but had never caused her pain in walking. An ulcer on the ball of the right foot had been there for seven months and had only recently shown signs of healing.

In her "early twenties" she began to suffer from shooting pains— "just like a knife going through"— mainly in the legs and to a less extent in the arms. Each pain lasted two or three seconds, and she would get some relief by standing still and squeezing the part affected. They occurred most frequently in the thigh and shin, and had never attacked the face, neck, or trunk. In wet weather they persisted on and off the day long. In addition, she suffered from pains in her feet which seemed to be of a different nature and to last longer. These ran along the outer side of the foot from ankle to toe. She said the shin on that side was often very tender to pressure.

For about the previous 20 years she had complained of

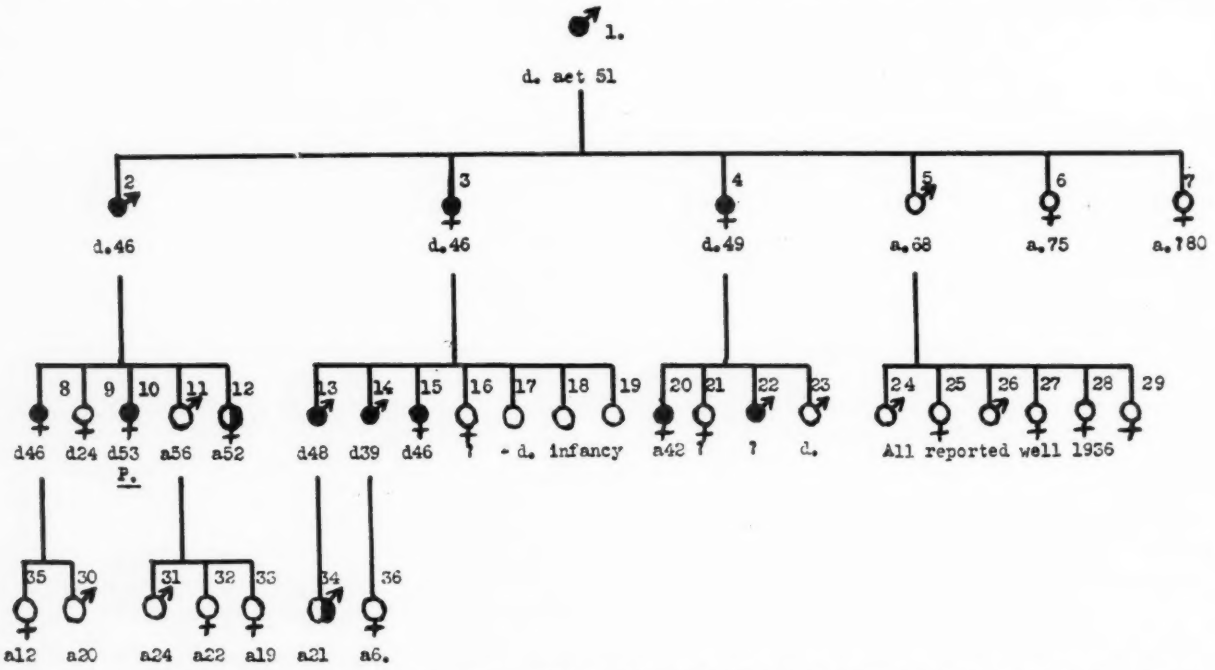


FIG. 1.—Chart of the R. family according to information available in 1936. P. is the patient described in the text. The numbering is as in the chart of Hicks (1922) with numbers 35 and 36 added.

a = alive, followed by age in years in 1936; d = dead, followed by age at death; ? = fate uncertain; ● = affected; 0 = unaffected; ◑ = tinnitus only.

headache which was always occipital, sometimes quite high up, and at others more over the upper part of the neck. Its character varied from a continuous ache to a rapid, shooting pain. It could be "dreadful". She had had one daily in the previous few months.

Deafness began in 1921 and had steadily increased, so that by 1936 she was almost completely deaf. There had been no tinnitus. She stated that she often felt that she might fall when going downstairs and had to hold on to the bannister. For five or six years she had been unable to walk in the dark without some support. Her gait had been unsteady for three years and she tottered while walking.

Seven to eight years earlier she had had to give up needlework as she could not feel the needle distinctly with her fingers. Proper feeling was absent in the hands, and she now could not say exactly what she was holding. For quite two or three years she had had no thermal sensation in the hands and had burned herself. In the previous six months blisters had appeared on many fingers—probably the results of scalds. She burned her right leg three years earlier, and lost the right little toe through a burn, which was quite painless, two years earlier. An ulcer on the left leg was due to a burn with a hot water bottle three months before admission to hospital and showed no sign of healing.

She had had pins and needles sensations in both hands and feet in the past but not at all latterly. She thought that muscular power in the arms was normal, but diminished in the legs. There had been occasional incontinence of urine but no pain, difficulty, frequency, or nocturia. She stated that the bowels were always regular and there had been no incontinence or urgency. Her nephew later stated that she had been liable to attacks of diarrhoea for some years but not in the months preceding examination. Her sight had deteriorated and she wore glasses.

She stated that her appetite had been good and she had had no indigestion. She had often been dyspnoeic on exertion, but without pain or tightness in the chest or oedema. Her sleep was variable, depending on the amount of pain. On the whole it was good. She was accustomed to retire to bed only in the early hours of the morning, and then to spend most of the morning in bed.

Her nephew, from whom much of the history was obtained, stated that her intelligence was variable. At times she would be very dull and could not grasp what was said without much repetition. On other days she seemed "quite normal". Her memory had latterly been bad. Her temper had been equable.

This patient had been examined by Dr. Hicks in August, 1921. He wrote (1922):

> "... right big toe showed evidence of old healed ulceration on the plantar surface; it was shorter than the left big toe. Knee and ankle jerks absent, supinator jerks natural, pupils reacted to light and accommodation, no nystagmus, slight Rombergism present. Sensation: tactile anaesthesia over first interdigital cleft on both feet; painful and thermal anaesthesia over lower parts of both legs.
>
> "Ears: slightly deaf for two years; both ears found to be plugged with cerumen. She heard much better after this was removed. Auditory nerve not tested on account of recent removal of cerumen."

The Wassermann reaction was not ascertained at that time.

Examination of the Central Nervous System.—The patient was a thin, poorly nourished woman of moderate height. Though thin, she was quite well preserved for her years and her hair was black without a tinge of greyness. She was not anaemic. She was severely deaf, and even with a long ear-trumpet conversation was very difficult.

She was quiet and reserved, but did not seem to be depressed. It was difficult to estimate her memory and intelligence: they appeared to be subnormal. Speech was monotonous, and high-pitched as a result of her deafness, but not otherwise abnormal.

She had occasional momentary attacks of pain in the legs and feet which made her wince and rub the affected part. They certainly suggested lightning pains. She also complained of an occipital headache.

Cranial Nerves.—The sense of smell was present in both nostrils. Vision was 6/12 R. and 6/18 L. uncorrected, the visual fields were full, the fundi and discs normal. Both pupils were smaller than usual, the right slightly smaller than the left, and both were slightly irregular. The reaction of the pupils to light and to accommodation was brisk and well held. There was no strabismus or nystagmus. Ptosis was not present. Hearing was diminished to perception of a very loud shout in either ear. Air conduction was greater than bone conduction on both sides. Weber's test showed no reference to either ear. No defect was found in the functions of the remaining cranial nerves.

Motor Function.—There was no demonstrable weakness in the muscles of the neck or trunk. Muscular development in the upper limbs was poor, and there was slight hypotonia on both sides, but no localized atrophy or weakness was detected. Coordination in the finger-nose test and in alternating movement was excellent.

The posture of the lower limbs was normal, but the muscles were all thin and hypotonic. Muscular power was, however, surprisingly good, and no weakness or localized atrophy was demonstrable. There was considerable unsteadiness and irregularity of movement in heel-knee and heel-shin tests.

Reflexes.—The biceps and supinator jerks were absent in both upper limbs but the triceps jerks were both brisk. A middle abdominal reflex was obtained on both sides. There was complete absence of knee and ankle jerks. No plantar response was obtained on either side. There was full control over the sphincters.

Sensation.—The patient was a difficult witness. The sense of pain was lost over both hands and lower third of the forearms (Fig. 2). There was some impairment as high as the elbow on each side, with a fading upper border. In the lower limbs the sense of pain was completely absent below the knees and impaired to some degree as high as the groin. Pressure pain was also

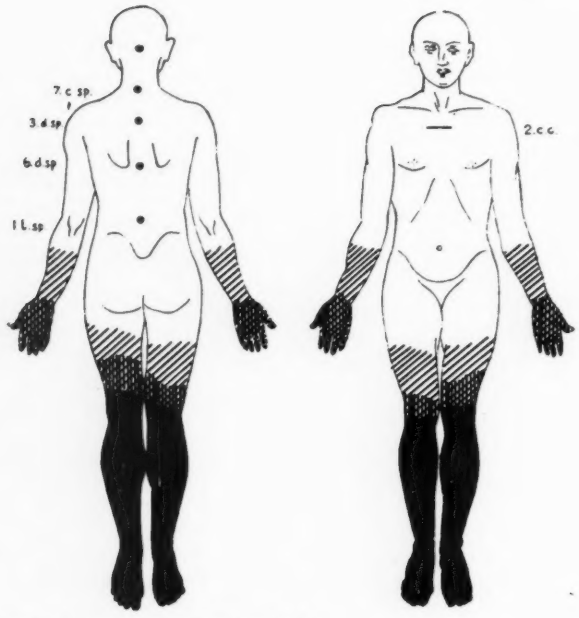


FIG. 2.—Chart of sensory loss in E.R.
The solid black area represents complete loss of all forms of sensation, the vertical shading complete loss of pain sensation, oblique shading loss of temperature sense. Impairment of temperature sensation was present in some degree over all the limbs and the trunk up to the level of the clavicles.

absent below the knee. In the proximal segments of the limbs and the lower parts of the trunk appreciation of pin prick was often delayed. The sense of touch was impaired in the fingers of both hands and absent below the knees on both legs. The sense of temperature was completely lost over the lower third of the forearm and hands, and below the middle of the thigh on both sides. The sense of vibration was diminished in the upper limbs and clavicles, and completely absent in the malleoli, knees, pelvis, and below the eleventh thoracic spine. The sense of position was present in the fingers of both hands, and absent in the toes and ankles on both sides, though the fact of movement was there appreciated. The posture of the knees was appreciated normally.

Trophic Changes.—The skin of the hands was of normal texture but there were some small corns in the flexures of the right thumb and index finger, on the pad of the second, and the side of the left index, and top of the little finger. The nails were a little brittle and pitted. When the feet were examined, it was found that the right foot was severely deformed. The right little toe was missing (burnt two years earlier) and the great toe had lost the proximal phalanx. The ball of the right foot was thickened. A small, punched-out ulcer, about 2 mm. in diameter, was covered by scaly epithelium and lay under the head of the first metatarsal. The fourth toe on the left foot had lost the nail and terminal phalanx. The skin of the sole was greatly thickened, but there was no ulceration on that side. The remaining toe nails were cornified.

On the inner side of the left leg at its middle there was an ulcer, 50 cm. by 30 cm., with a sharp serpentine edge, unhealthy pink granulations, and purulent discharge. Romberg's sign was markedly positive; her gait was irregular, she staggered in walking, and had a tendency to seek support from surrounding objects.

The ulnar and peroneal nerves were palpated and did not appear thickened or tender. There was no muscular tenderness.

General Examination.—The pulse was regular and the vessels soft. Both dorsalis pedis arteries were palpable. The heart was not enlarged and the sounds were normal. No abnormality was found in the chest or abdomen. Bifid spines could be palpated from D 12 to L 2, but there was no other abnormality, and no limitation in movement. All other joints were normal. No abnormality in endocrine function was detected.

No glycosuria or albuminuria was found during the hospital admission.

Lumbar puncture revealed a clear cerebrospinal fluid under normal pressure, with normal dynamics. There were no cells seen; the total protein was 40 mg. per 100 ml.; the Wassermann reaction was negative. The blood W.R. was negative.

Gastric analysis revealed complete achlorhydria but no other abnormality.

The blood count gave 5,100,000 R.B.Cs per c.mm.; haemoglobin, 104%.

On radiological examination the loss of the phalanges seen on clinical examination was confirmed, and atrophic bony change in all the phalanges and metatarsals of both feet seen. There was no abnormality seen in radiographs of the temporal bones or spine.

Clinical Course.—The ulceration on the left leg, and the small perforating ulcer on the right foot healed completely with rest in bed for a month. The patient complained bitterly of lancinating pains in the lower limbs and in the back of the head and required regular sedation for these. She was discharged to a convalescent home and when next seen some two months later was ill with bronchopneumonia to which she succumbed.

Necropsy

Necropsy was performed by Dr. J. G. Greenfield who found a thick-walled cavity about 2 cm. in diameter at the apex of the right lung. This showed no evidence of tuberculosis in the wall, and appeared to be of pyogenic origin. Elsewhere the lungs were healthy. The gall bladder was shrunken down over a few calculi and the wall was adherent to the duodenum. In the pelvic colon there was diverticulitis with the formation of one or two small abscesses in the mesocolon. The bladder contained mucopus and the wall was intensely inflamed. Both kidneys also were very inflamed with early abscess formation in places. No evidence of amyloid degeneration was seen in sections of any organ of the body cavity.

The brain was small, weighing only 915 g. The acoustic nerve was thin by comparison with the facial nerve and pars intermedia which appeared normal.

The spinal cord was removed along with the cervical and lumbo-sacral plexuses on the left side. The posterior roots of the cauda equina were grey and atrophic and

the nerves were very thin, especially the sciatic and ulnar. There was no obvious deformity of the spine. The deformity of the feet was not subjected to further examination.

A series of ganglia and nerve roots, with pieces of peripheral nerve and muscle, were removed for special examination by the author. It was noted at the time that the first sacral and fifth lumbar ganglia appeared shrunken and fibrotic to the naked eye, and the attached dorsal roots particularly atrophic.

Microscopical Examination.—Transverse sections of the spinal cord and brain stem were cut at several levels. In sections of the lumbar cord stained for myelin (Pal-Kultschitsky method) there was a considerable loss of fibres in the dorsal columns, especially in Flechsig's posterior root zone (Fig. 3). At higher levels the fasciculus gracilis was shrunken and partially demyelinated throughout but still contained many intact myelin sheaths. At the lowest cervical levels there was slight pallor at the root entry zone but the fasciculus cuneatus appeared intact in the upper cervical segments.

There was no evidence of spina bifida, syringomyelia, or dysraphism. The meninges appeared normal. In sections stained by the Nissl method the anterior horn cells in the lumbo-sacral and cervical segments were of normal appearance. There was no abnormal pigmentation, and no chromatolysis. The anterior roots stained well in Weigert sections, but the dorsal nerve roots had lost many fibres, especially at C 8, L 5, and S 1 levels.

Sections of the nerves and ganglia were stained by iron-haematoxylin and Van Gieson, haematoxylin-eosin, and cresyl-violet. Sample sections from these blocks were stained by the Gros-Bielchowsky method. Other blocks were mordanted and stained by Pal-Kultschitsky method. Some sections of ganglia were stained with Congo red. Frozen sections of nerve roots and ganglia were stained for fat with Scharlach R.

The peripheral nerves and nerve roots showed a considerable loss of nerve fibres, both in sections stained for axis cylinders and those stained for myelin sheaths. The sciatic nerve had lost about one-third of its fibres at mid-thigh level. The patchy distribution of the loss was notable. The bundles of the median nerve in the forearm had a similar appearance. The posterior tibial nerve in the popliteal space had lost quite two-thirds of its fibres, and it was here clear that the remaining fibres were uniformly large (Fig. 7). Lower down, near the ankle only three or four sound fibres remained in each section of some bundles, and an estimated total of less than one-third of the nerve fibres was found in all muscular nerves. Except for an occasional fragment of axis cylinder (Fig. 4) or chain of such fragments, or myelin droplets, the remaining fibres appeared normal in structure. There was no evidence of the fine fibrils seen in regenerating nerves. Densely packed columns of Schwann cells, with mild endoneurial fibrosis were all that remained of the absent fibres. The proximal nerve trunks and plexus bundles also showed patchy loss of nerve fibres, and here and there a fibre in degeneration. There was no cellular or other infiltration, and no change in the perineurium or epineurium. The blood vessels were normal. The appearance of the nerves was therefore that of a Wallerian degeneration of long duration with recent changes in a few isolated nerve fibres.

Section of muscle (gastrocnemius, peroneal muscles) showed normal muscle fibres and connective tissue. There was no evidence of atrophy, either of a neural or myopathic type. The blood vessels appeared normal.

Nerve Roots and Ganglia.—Sections of the nerve roots and ganglia revealed profound changes. These were most severe in the first and second sacral, and last two lumbar ganglia. There were less severe changes in the eighth cervical and first thoracic ganglia. There was great loss of ganglion cells with severe degeneration of both the peripheral and central parts of the dorsal nerve roots (Figs. 5 and 8). The ventral nerve roots were intact throughout (Fig. 6). In the first sacral dorsal root ganglia of both sides only 10 to 20 ganglion cells remained in each section (Fig. 9). The remaining ganglion cells, impregnated with silver, showed a great proliferation of subcapsular dendrites (Fig. 11). This change (Fig. 12) was also common in the cervical ganglia examined (C 5, C 6, D 1). In these ganglia there was some loss of ganglion cells, but milder than in the lumbo-sacral region.

In sections stained with haematoxylin-eosin the capsules and satellite cells of some of the remaining nerve cells had undergone mild proliferation. In sections impregnated with silver and counterstained with haematoxylin it was clear that such neurons had developed dense subcapsular networks. Less than 10% of the remaining ganglion cells appeared normal. In all sections only three or four cells exhibited vacuolation and nuclear shrinkage. Fat stains showed no abnormality. Pal-Kultschitsky sections confirmed the great loss of fibres and ganglion cells shown by other methods. Rarely a few droplets indicated recent degeneration of an isolated fibre. The motor nerve roots, as they passed the dorsal ganglia, showed robust normal axis cylinders and myelin (Fig. 6), with no evidence of loss of fibres.

The capsules of the dorsal root ganglia appeared normal as also were the vessels in and near the ganglia. The first sacral and lower lumbar ganglia showed a generalized increase of connective tissue. There was some proliferation of arachnoidal tissue at the point of reflection of the pia-arachnoid from nerve root to dural sheath, but no evidence of strangulation of the " radicular nerve " of Nageotte. In the ganglia the increase of perineurial fibroblastic connective tissue was diffuse, but was intense in degree only in the first sacral ganglia, where it took a pink stain with Van Gieson.

Residual nodules in the form of dense clumps of five to 15 darkly staining, spindle-shaped nuclei in an irregular star formation were common in the cervical ganglia, moderately frequent in the first dorsal ganglion, but very few remained in the sacral ganglia. In the first sacral ganglia the ganglion cells had disappeared without leaving any trace, unless they were represented by clear hyaline bodies which were scattered throughout all the sacral ganglia and were seen in small numbers in the lower lumbar and cervical ganglia. These hyaline bodies each showed some pale, elongated and distorted nuclei within them, but were not encapsulated. These bodies

FIG. 3.—Familial perforating ulcer in Case E.R. Section of first lumbar segment of spinal cord. Pal-Kultschitsky method for myelin.

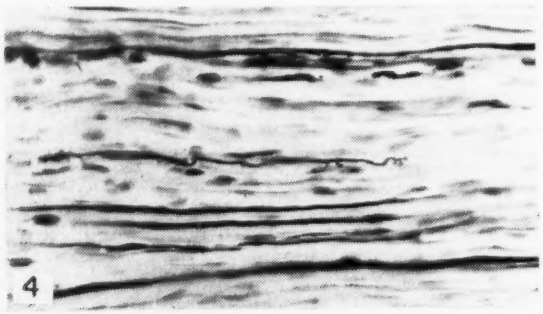


FIG. 4.—From a longitudinal section of sciatic nerve. Gros-Bielschowsky method for axis cylinders.

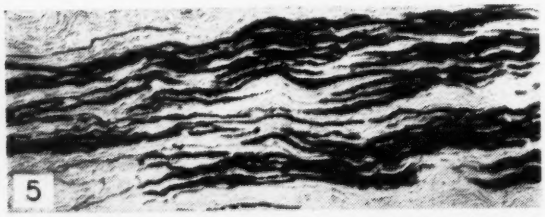


FIG. 5.—Fourth sacral dorsal root just proximal to the ganglion. Pal-Kultschitsky method for myelin.

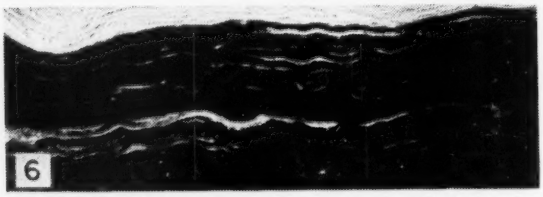


FIG. 6.—Fourth sacral ventral root just proximal to the ganglion for comparison with Fig. 5 (stained by the same method).

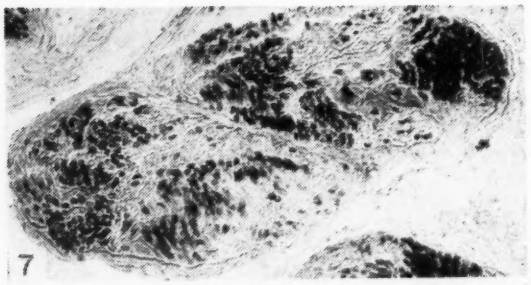


FIG. 7.—Transverse section of one fasciculus of the internal popliteal nerve in the popliteal space ; same method.

FIG. 8.—From a section of the first sacral nerve root ; same method.

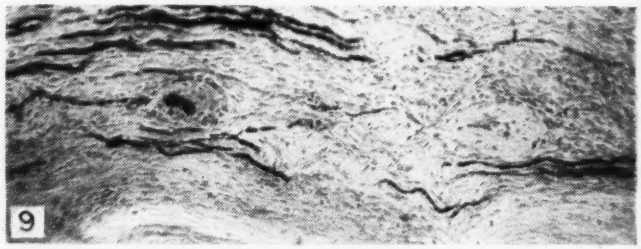


FIG. 9.—First sacral dorsal root ganglion stained by the same method. A ganglion cell is seen to the left, and a hyaline mass to the right of the centre.

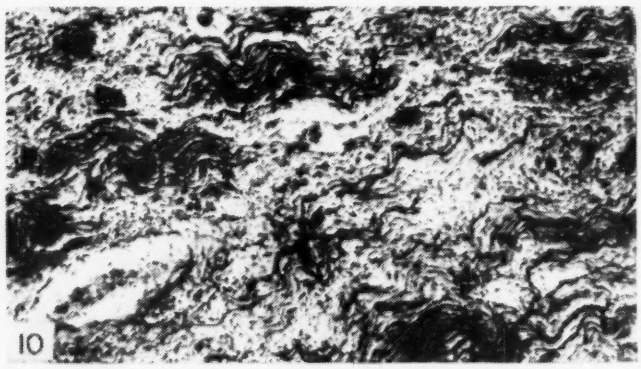


FIG. 10.—First sacral dorsal root ganglion stained by the Gros-Bielschowsky method and counterstained with haematoxylin to show residual ganglion cells, fibroblastic reaction, and two small arterioles with hyaline (amyloid) degeneration of the media.

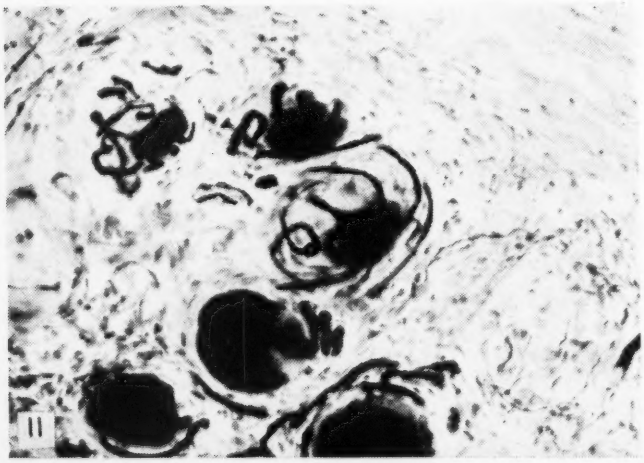
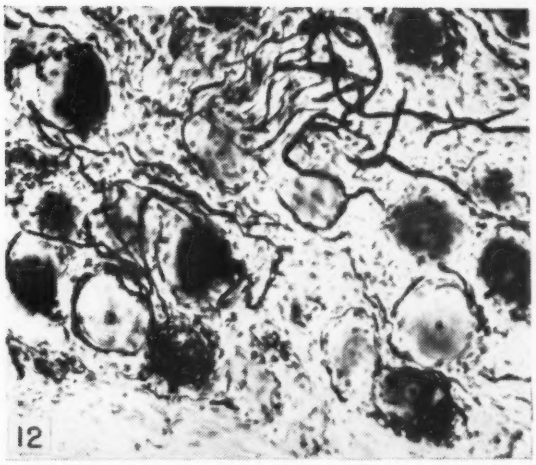


FIG. 11.—First thoracic dorsal root ganglion stained by the Gros-Bielschowsky method and haematoxylin to show residual ganglion cells with subcapsular proliferation of dendrites. At lower right is a hyaline mass penetrated by a coiled, fine, beaded axis cylinder.



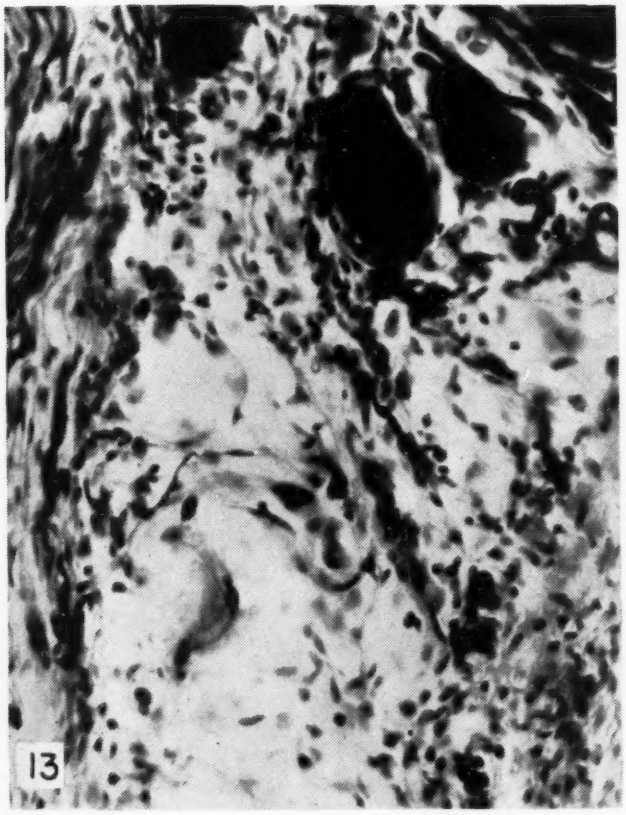


FIG. 12.—Eighth cervical dorsal root ganglion (same method) to show mild reactive changes in ganglion cells.

FIG. 13.—First thoracic dorsal root ganglion (same method) to show a large hyaline mass in the left lower part of the illustration, with convoluted capillary core and endothelium, and also a fine axis cylinder passing through it. There is an unusually intense tissue reaction surrounding this mass. The large impregnated objects are nerve cells and fibres.

FIG. 14.—As Fig. 13 to show cellular details in another mass.

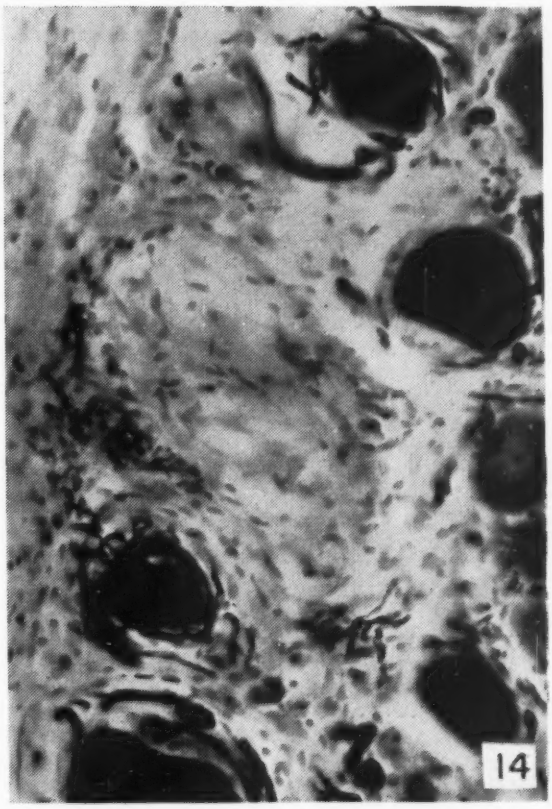
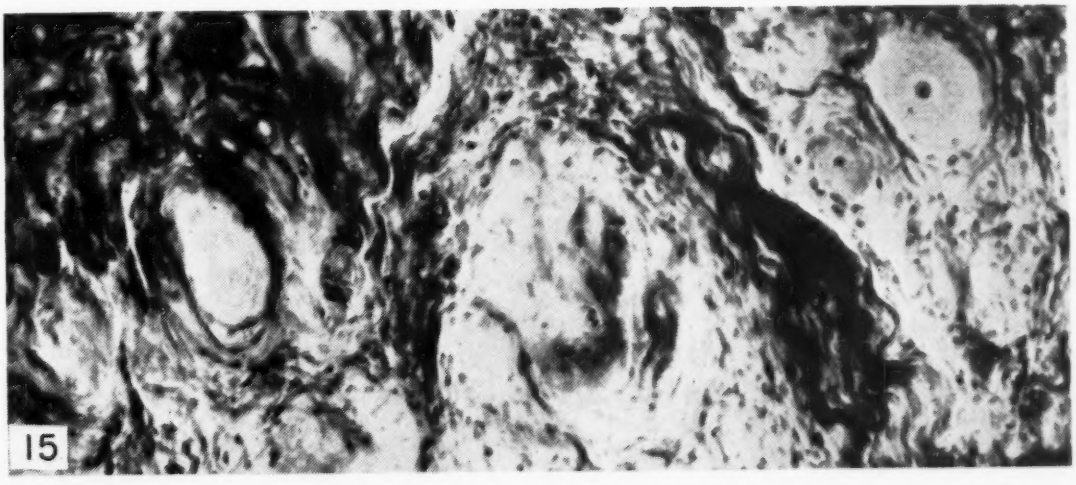


FIG. 15.—First thoracic root ganglion stained with Congo red and haematoxylin to show the contents of a large hyaline mass in the centre of the figure. Another, with dark convoluted contents, occupies the whole left upper corner. The pale object in the centre of the left half of the figure is a nerve cell, and others are seen to the right. Collagen is also stained.



were most numerous between the surviving ganglion cells just under the capsule of the sacral and first dorsal root ganglia (Figs. 11 and 14). The clear substance which filled them failed to stain with haematoxylin, eosin, Pal-Kultschitsky, or fat stains, and was not impregnated with silver. These bodies stained diffusely faint yellow with Van Gieson and light blue with cresyl-violet, but the latter was not attempted until some months after fixation. In formalin-fixed, celloidin-embedded material they stained from light pink to deep red with Congo red, and this dye revealed convoluted tubular cores and dark partitions in many of the masses (Fig. 15). With silver impregnation and haematoxylin it was sometimes obvious that capillary endothelium formed a central core to one or other of these masses (Fig. 13). With Congo red many of the masses had a whorled tubular central structure, strongly suggesting that the hyaline or amyloid mass had accumulated around a capillary. The ill-defined convoluted basis of such a mass as is seen in the upper left corner of Fig. 15 may represent occluded capillaries. In the centre of Fig. 15 a similar tubular structure merges into a more lightly stained mass of the material. Thus Congo red was the only dye which revealed anything of the structure of the hyaline material, which otherwise presented the appearance shown in the centre of Fig. 14. In a few instances, however, some substance which stained only with Congo red was present under the capsule of a surviving but altered ganglion cell. The arterioles and larger blood vessels of the ganglia appeared normal in every respect.

In the less severely affected cervical ganglia hyaline bodies were rarely seen, and only a hyaline thickening of some of the smaller vessels (Fig. 10) represented the change which was so conspicuous in the sacral ganglia. There were no hyaline bodies or altered capillaries in the nerve roots, peripheral nerves, spinal cord, or other tissues examined.

Silver impregnation showed that finely beaded nets of dendritic processes surrounded and penetrated some of the hyaline masses, as in Figs. 11 and 13. Many were completely devoid of nerve fibres (Fig. 14). Such nerve fibres appeared to belong to wandering branching processes of the dendritic proliferation of reacting ganglion cells.

In summary therefore, the most widely distributed changes in the dorsal root ganglia were dendritic proliferation and the presence of residual nodules, both indicating relatively recent cell damage. In the first sacral and first thoracic ganglia loss of ganglion cells was severe and residual nodules were few, and in addition many hyaline masses which gave a weak staining reaction for amyloid were present. In these ganglia there was also a moderate fibroblastic reaction. The amyloid masses appeared to have accumulated around capillary vessels, most of which were no longer patent. There was a mild tissue reaction to these masses, but no giant cells were seen. There was no such change in the vessels of the kidney, spleen, or liver, or in the ailmentary tract.

Discussion

The findings described above establish that the cause of " hereditary perforating ulcer of the foot " in the family originally reported by Hicks (1922) is a degenerative condition of dorsal root ganglia. Of 36 members of this family 11 certainly suffered from the disease in 1936. All these 11 suffered from trophic ulceration of the feet and deafness, and of these seven suffered from shooting pains closely resembling lightning pains, four from recurrent chronic diarrhoea. The upper limbs were known to be affected late in the disease in two. Two additional members suffered from tinnitus, which probably heralded the onset of further symptoms. The striking feature in all was the predominant loss of sense of pain in the feet. Though the sensory dissociation had suggested a diagnosis of syringomyelia to Hicks, and in similar cases, to Bruns (1903), Göbell and Runge (1914), Guillain and Thévenard (1929), Wagner (1932), Smith (1934), and Mueller and Sugar (1943), that condition was not present in our case. Similarly there was no evidence of deformity of the cord or nerve roots due to spina bifida occulta, or dysraphism, as was suggested on clinical grounds by Schultze (1917), Riley (1930), and Mulvey and Riely (1942). The case of Miss R. appears to be the first reported with a pathological examination.

All these cases presented evidence of loss of pain and temperature sensation in the feet in an irregular but generally symmetrical area which in many cases extended to the middle of the leg, and rarely as high as the knee. Only in the cases of Göbell and Runge was loss of sensation difficult to demonstrate but it was noted that a very strong stimulus was necessary to elicit pain in the foot. If sense of touch were affected at all, it was diminished over the great toe, or a small area of the foot. Sense of vibration or position is usually not lost. The ankle jerks were absent by the time trophic disorders appeared and in many cases the knee jerks were also unobtainable. In the first case of Mulvey and Riely, however, sluggish knee and ankle jerks were obtained. Diffuse aches are commonly described, often as " rheumatism ", but lightning pains have not previously been noted. There has been usually no motor weakness or atrophy, but Bruns described weakness and slight atrophy in one case, and Riley reports others. Control of the bladder has not been affected except in one case of Bruns. The pulsation of the blood vessels in the feet, if mentioned, has been present, but many have noted coldness of the feet and in some, of the hands, long before other symptoms. The upper limbs have not been affected in other families, and deafness appears to be a feature which is unique in the R. family. The trophic disorder has been limited to the soles of the feet in all the families described, but spread of infection to involve bones of the tarsus has often necessitated amputation.

It is therefore evident that the general clinical features of familial perforating ulcer are all capable of explanation as the result of a chronic neuritic process affecting the lumbo-sacral nerve roots. The exception to this statement is a family of three siblings reported by Verhoogen and Vandervelde (1894) in one of whom necropsy was held to demonstrate syringomyelia. These patients suffered from trophic ulceration of the hands, severe pains in the limbs and head (two cases), severe symmetrical loss of pain and temperature sense in the hands (and in two cases in the lower limbs with loss of ankle jerks, weakness and contractures), but without deafness. The one necropsy revealed a small fissure in the grey matter of the spinal cord which was interpreted as a syringomyelic cavity. Schlesinger (1902) in his monograph on syringomyelia did not accept this as evidence of that disease, which he denies may be familial. I would agree that the description of Verhoogen and Vandervelde is unconvincing, and note that the dorsal root ganglia were not examined. The dorsal columns of the spinal cord showed some degeneration, and degenerative changes in the nerves and muscles of the limbs were found. I therefore consider it probable that the pathology in the family described by Verhoogen and Vandervelde was the same that I have described. It should be emphasized however that van Bogaert (1934) has later described syringomyelia with classical distribution in the upper limb, in two sisters, in association with features of Lindau's disease. This disorder is certainly unique. It did not present as symmetrical trophic ulceration.

The entity of myelodysplasia, or dysraphism, appears to date from the conception of Fuchs (1909) who emphasized the lesser manifestations of spina bifida, with their characteristics of unvarying enuresis, syndactyly, hypertrichosis and naevi of the lumbar region. The subject has recently been fully discussed by Bremer (1937), and by Mulvey and Riely (1942), but it is evident that dissociated sensory loss sufficient to lead to trophic disorder would require a more extensive cord lesion than was postulated for myelodysplasia. The outstanding requirement of enuresis since birth, which we would consider inseparable from lumbosacral dysplasia, has been absent in familial perforating ulcer.

It is necessary to draw a sharp distinction between this slowly progressive disorder, " hereditary perforating ulcer ", and the syndrome of " congenital universal indifference to pain " of which a typical case has been recently reported by Boyd and Nie (1949). Earlier cases were described by Ford and Wilkins (1938). In this condition no hypalgesia or other neurological sign is found, and though trophic disorders arise, they may be in any part of the body and are all traceable to the indifference of the patient to the presence of pain. Concomitant disturbance in the mechanism of speech in two cases suggested the possibility of a cerebral defect in recognition of pain. The disease reported here, in contrast, presented a true analgesia, primarily presenting in the cutaneous segments of the lumbo-sacral region.

The condition which most closely resembles hereditary perforating ulcer is the chronic symmetrical form of sensory neuritis which occurs in diabetes (" pseudotabes diabetica "). This condition, of which an excellent description is given by Pavy (1904), occurs only in extremely chronic diabetics. More extensive loss of sensation to pain and temperature than to touch, beginning commonly in the distribution of the fifth lumbar and first sacral roots, leads to trophic ulceration and arthropathy in the feet. The sphincters are involved only late in the disease. Lightning pains and ataxia are common. Deafness is not a feature. The absence of glycosuria in many examinations of at least three members of the R. family, and in many of the cases reported in the literature, makes it certain that diabetes has no part in hereditary perforating ulcer.

Sensory Dissociation.—It has been clear in all the previous cases reported that the loss of sensation to pain is greater than that to touch, and the loss to temperature greater than that to pain. The presence of this dissociation in this disease, so characteristic of damage to the grey matter of the spinal cord, demands some explanation in the absence of such damage. Two considerations suggest themselves. First, the striking loss of smaller ganglion cells and smaller nerve fibres in the most affected ganglia and nerve roots means the loss of the smaller myelinated fibres which are commonly regarded as those serving pain. Some small cells were still present, however, even in the most severely affected ganglia. Secondly, it is well known that affection of any single nerve root or sensory ganglion causes an area of sensory loss which is more extensive to temperature and pain than it is to touch. In the early stages of this disease it would appear from the clinical descriptions that it is mainly the first sacral nerve root that is affected. The corresponding sensory loss would then be of dissociated type. That this second explanation is in part valid is shown in the lesser degree of dissociation as more roots are affected, as in the case here reported (Fig. 2). If the cause of dissociation were an exclusive attack on the smaller dorsal root pain and temperature neurons, one would expect the dissociation to become more obvious as the affection progressed, whereas in the severe stage of this

disease, all sensation was affected. It is concluded that the sensory dissociation is prominent in this disease because it is primarily a radicular affection.

Deafness.—Both temporal bones were fixed in 10% formol saline and examined histologically by Mr. Philip Scott at the Ferens Institute of the Middlesex Hospital. He reported as follows :—

> " Sections show a marked reduction in the number of cells in Scarpa's ganglion. The cells of the spiral ganglion show degenerative changes and appear to be reduced in numbers, as also are some of the ciliated cells of the organ of Corti. There is some vacuolation in the stria vascularis."

This atrophy of the cochlear and vestibular ganglia parallels the atrophic process here described in the spinal ganglia. The clinical findings were of nerve deafness and in another patient in this family the findings were consistent with " primary cochlear degeneration " (Case 20, Appendix).

Weigert-Pal transverse sections of the upper medulla showed that the cochlear nerve as it entered the brain stem was fairly well myelinated but it may well have been shrunken as the sections, being longitudinal to the nerve, did not permit of any estimation of its thickness. The appearances were consistent with the number of residual cells in the spiral ganglia, which were probably still able to maintain the nutrition of their axons, and with the fairly solid, well-myelinated cochlear nerve seen in sections of the internal auditory meatus.

Unfortunately the sections of the brain stem did not go so far in a rostral direction as the entry of the vestibular divisions.

Neurogenic deafness has not been mentioned in other families reported. Deafness has, however, been reported in association with peroneal muscular atrophy by Campbell (1900), Taylor (1913), Biemond (1928), and Somogyi and Fényes (1931). It was associated with chronic hypertrophic interstitial polyneuritis in a case of Dejerine and Thomas (1901), and was found by Refsum (1946) in two of five cases of hereditary ataxic polyneuritis. It is therefore not a specific symptom, but may nevertheless represent a common factor in all these various familial and hereditary neuritides.

Pathogenesis of Perforating Ulcer.—The prominence of perforating ulcer in this family, and in the other families reported, is clearly related to the loss of pain sensation in the feet, and in some cases in the hands. In one case (Case 20, Appendix), Dr. Hicks found " slight loss to thermal sensation " but no loss to pain or touch. The demonstration of small, patchy areas of dissociated pain loss is, however, sometimes exceedingly difficult, for the patient can often distinguish between the point and head of a pin by touch alone, as in many cases of syringomyelia, without any appreciation of pain. It is concluded that trophic ulceration is dependent upon loss of pain sense and not upon the absence of any specific " trophic " nerves such as were proposed by Lancereaux (1894) and others. Indeed, the remarkable condition of " congenital universal indifference to pain " mentioned above proves clearly that trophic disorder is dependent upon absence of *lack of reaction to pain* and not upon any quality of pain sensation. In my case, and many others of familial perforating ulcer, the ulceration healed rapidly with rest, so that there appears no cause to doubt the widely held opinion that a perforating ulcer begins with sepsis in a corn, and assumes its characteristic deep and persistent necrosis only because the absence of pain sensation prevents the protection and adequate rest necessary for healing. Thus the perforating ulceration is regarded only as a result of loss of pain sensation in weight-bearing areas.

In the cases recorded in the R. family there was no evidence of neuropathic joint change. Such changes have been noted in the family reported by Bruns, and also that of Mueller and Sugar, and appeared to be precipitated by trauma to the ankle.

The pains complained of by these patients resemble lightning pains. They are presumably due to the damage to the root ganglia and have a root distribution. The condition is, however, quite distinct from tabes dorsalis, not only in the absence of pupillary abnormality, but also in the essential pathological finding that the nerve fibre degeneration occurs both distal to and proximal to the ganglion. In tabes dorsalis the degeneration is entirely proximal, as I have verified for myself in two cases. The lightning pains are to be regarded as root pains, both in tabes dorsalis and in hereditary perforating ulcer.

Relationship to Neurofibromatosis or Other Forms of Chronic Peripheral Neuritis.—The finding of large hyaline masses in the dorsal root ganglia at once called to mind the ganglionic changes reported in some cases of von Recklinghausen's disease. Two types of change occur in neurofibromatosis. One is a great thickening of the outer sheath of the dorsal root ganglion, which is continuous with the perineurium of the peripheral nerve. This is a simple fibroblastic proliferation. The other type affects the capsule of dorsal root ganglion cells, producing an onion appearance of laminated capsule cells enclosing a smaller more lightly stained whorl of proliferated satellite (Schwann) cells. Since such a ganglionic neuroma is extremely rare, an illustration is included (Fig. 16) from a

patient suffering from generalized neurofibromatosis for comparison with the masses found in the present case. It is clearly quite different. Neither type of change was found in our case of familial

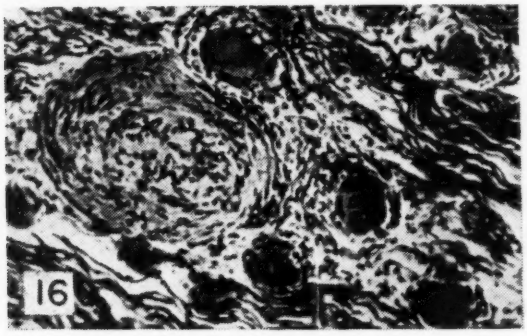


FIG. 16.—Dorsal root ganglion from a case of generalized neurofibromatosis, stained by the Gros-Bielschowsky method and haematoxylin, to show the structure of a neurofibroma of a ganglion cell, in contrast to the hyaline (amyloid) masses in the case of hereditary perforating ulcer. Note the separate proliferation of capsule and satellite cells.

perforating ulcer. The hyaline changes found in the ganglia of the case reported here were not found in our case of neurofibromatosis, or our cases of tabes dorsalis. Further, there were no changes in the nerve roots, or peripheral nerves, resembling either neurofibromatosis or the progressive interstitial hypertrophic neuritis of Dejerine and Sottas. The neural changes were of a simple degenerative kind. There was no evidence of periarteritis nodosa. A subacute degeneration of the dorsal root ganglia, associated with pulmonary carcinoma, has been reported (Denny-Brown, 1948) in two patients, in one of whom deafness occurred. The condition differed from that reported here in many respects, but indicates that the dorsal root ganglion cell may have a specific susceptibility to neuritic damage. The absence of degeneration of muscles or motor nerves in hereditary perforating ulcer serves to differentiate it completely from classical peroneal muscular atrophy. Refsum (1946) has recently described two families with ataxic polyneuritis, with some resemblance to peroneal muscular atrophy, but in addition a mixed sensory and cerebellar ataxia, and atypical retinitis pigmentosa. In three of five cases there was pupillary abnormality, and in three the protein in the cerebrospinal fluid was increased. Trophic changes were not found, though two patients had epiphysial dysplasia. My case had no resemblance to the disease reported by Refsum, which appears to be more closely allied to the syndrome of Roussy and Levy (1926). On the other hand, severe peripheral sensory disorder of radicular type has occasionally been reported in association with peroneal muscular atrophy, as in Charcot's original non-familial case Sultz of which the post-mortem examination was reported by Marinesco (1894). The changes in the dorsal nerve roots and dorsal columns of the spinal cord reported by Marinesco closely resemble those found in the present case. The case of Bruns and of Riley, discussed earlier, appear also to combine peroneal muscular atrophy with severe radicular sensory disorder. Such cases appear to be connecting links between the classical radicular type of peroneal muscular atrophy at one extreme, and the purely sensory radicular neuropathy described here. Spillane (1940) has described a family presenting many members with the Roussy-Levy syndrome of familial pes cavus and areflexia, with one example of cerebellar ataxia and dysarthria resembling Friedreich's ataxia but without nystagmus, and three presenting muscular atrophy resembling peroneal muscular atrophy. Spillane therefore questioned the specificity of hereditary spinal degenerations. I prefer to classify the Roussy-Levy syndrome as a separate entity with unproven, but probably spinal pathology, and to group the classical form of hereditary peroneal muscular atrophy, with or without sensory change, and the pure sensory radicular sensory syndrome presented here, as hereditary radicular degenerations which remain true to type within each family concerned.

Amyloidosis.—The accumulation of amyloid in the liver, spleen, kidneys, and heart is a well known sequel to chronic purulent disease. The absence of such accumulations in the case reported is clear evidence that such amyloid changes as were found were not related to the chronic inflammation of the feet. The nervous system appears to have an immunity to such collections of amyloid when they do occur. Rarely the blood vessels of the peripheral nerves, especially the pelvic plexus, have been reported to show collections of amyloid, and in most cases no damage to nerve fibres has resulted (Belokrenitsky, 1911; Königstein and Spiegel, 1924; Kernohan and Woltman, 1942). De Navasquez and Treble (1938) reported a case of chronic peripheral neuritis in a man aged 36 who had suffered from diarrhoea for two years. Amyloid deposits were found in the peripheral nerves and ganglia as well as in internal organs. Kernohan and Woltman report a further case in a man aged 50 who had had lymphadenopathy for three years, aching pains in the abdomen and extremities, and peripheral neuritis for four months. There had been one attack of diarrhoea three months before death. All tissues, including the peripheral nerves but excluding the central nervous system, showed

extensive amyloid change. We have encountered two similar cases and also had the privilege of examining the material from De Navasquez and Treble's case. The appearance of amyloid in the peripheral nerves in such cases was very distinctive, for large irregular masses of the substance, usually with remnants of endothelial cells, lay between the nerves fibres, which were certainly as severely damaged as in our own cases. In places red blood corpuscles within an endothelial core revealed that the masses had collected around capillaries. In these cases there were also accumulations in the dorsal root ganglia, where they appeared both as isolated nodules and as cuffing to small blood vessels. One of my cases closely resembled that of Kernohan and Woltman. The other was a woman, M.L., aged 56 years, who had suffered from progressive unsteadiness and ataxia of the legs for one year, with paraesthesiae and later numbness of the feet. For five months there had been tingling, numbness, and clumsiness of the hands. In the last three months diplopia and bilateral deafness had appeared. Neither pupil reacted to light, there was ptosis and bilateral nerve deafness. There was no motor weakness or muscular atrophy, but the knee and ankle jerks were absent. There was severe loss of all forms of sensation in a glove and stocking distribution below the mid-thighs and wrists, with a fading upper border. The cerebrospinal fluid was normal in every respect (protein 40 mg. per 100 ml.). The Wassermann reaction was negative in blood and cerebrospinal fluid. The blood count was normal and a fractional test meal revealed normal free acid. There was no albuminuria. Necropsy revealed a generalized amyloidosis in every section of peripheral nerves and dorsal root ganglia. Since some of the masses of amyloid in this case closely resembled those found in my case of hereditary perforating ulcer an illustration (Fig. 17) of them is included for comparison.

It is therefore remarkable that amyloidosis can produce chronic progressive sensory neuritis and deafness. In the case of amyloid peripheral neuritis the ganglionic nodules were more numerous, more rounded and simply displaced neighbouring tissue, and there were no subcapsular collections. The general appearance was not identical with those of the ganglia of the case of hereditary perforating ulcer, but the vascular changes were the same, and some nodules had the same appearance in both diseases. These differences may, however, be only a matter of chronicity. De Navasquez and Treble reported subcapsular accumulations in their case. The case of hereditary perforating ulcer certainly had very few ganglia thus affected, and no amyloidosis of the peripheral nerves or other organs examined and thus differed greatly from the cases of amyloid neuritis I have mentioned.

The hyaline substance found in these ganglia raises precisely the same difficulty that Warren (1930) has discussed in relation to the hyaline degeneration of the islets of Langerhans in diabetes mellitus. Warren found a positive amyloid reaction in 14 of 51 cases, in the absence of generalized amyloidosis. In the latter condition the islands, like the dorsal root ganglia, are not involved as a rule. Hereditary perforating ulcer was not associated with diabetes, though it is remarkable that some chronic diabetics develop a progressive ganglionic degeneration involving the dorsal root ganglia, especially of the fifth lumbar roots, with shooting pains, and trophic ulceration of the feet. In the ganglia of two such cases which we have examined there was a generalized reactive proliferation of subcapsular dendrites, but the loss of nerve cells was not comparable to that in hereditary perforating ulcer and no hyaline or amyloid change was found.

The hyaline masses in the case of hereditary perforating ulcer showed a fainter staining reaction to cresyl-violet than do those of recent amyloid disease. They did not however present the staining reactions of mucoid, fatty, or other forms of degenerative material. Amyloid deposits in nervous tissue are evidently a capricious phenomenon, and cases of isolated amyloid deposition in the brain have been reported by several authors reviewed by Kernohan and Woltman. Until the cases of De Navasquez and Treble, and Kernohan and Woltman were reported it was not considered to be capable of causing damage to nerve fibres. The great disorganization of capillaries that is caused however must result in anoxia, which may be related to the mechanism of lightning pains in the disease under discussion. The subcapsular material present in some dorsal ganglion cells in the present case would offer more direct damage to the neuron. It is debatable whether the accumulation of amyloid is the primary feature of the disease, or is secondary to degenerative changes. I do not consider it to be the primary disorder, for many of the dorsal root cells

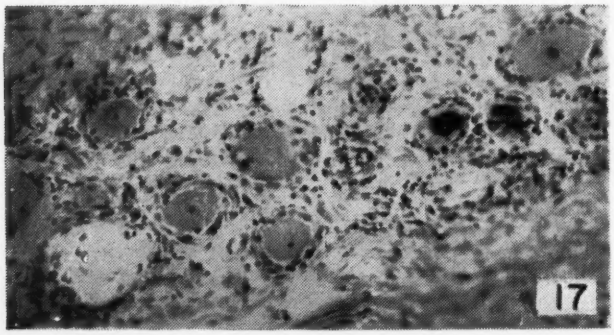


FIG. 17.—Dorsal root ganglion from case M.L. Same method. Masses of amyloid are seen at the lower left and upper centre of the figure.

show evidence of reaction to disease by proliferation of subcapsular dendrites where no such change in the capsular cells has occurred. Thickening of the walls of vessels is commonly found in relation to syringomyelic cavities in the central nervous system, for example, and Fischer and Holfelder (1930) report amyloid degeneration in the blood vessels of an area of previously irradiated brain. The amyloid bodies in my case of hereditary perforating ulcer were present only in the most severely affected ganglia, whereas ganglion cell damage and subcapsular proliferation of dendrites were widespread in nearly all the ganglia examined.

Recurrent diarrhoea is a common accompaniment of amyloidosis, and it is of interest to note that the patient here reported and also Cases 2, 13, and 8 were known to have suffered from intermittent diarrhoea. In Case 2 it occurred for two weeks as a terminal event, in Cases 8 and 13 repeatedly for years, and in Case 10 (that reported here) in bouts from 1933 to her death in 1936. This immediately suggests the possibility of intestinal amyloidosis, but this was certainly not present.

I conclude that hereditary perforating ulcer is a primary degenerative disorder of the dorsal root ganglia, with selective incidence on those ganglia which serve the extremities. In the R. family secondary amyloid degeneration of blood vessels was prominent in severely affected ganglia, but this is regarded as a phenomenon secondary to some unknown metabolic defect. Though the disease has affiliations with other kinds of degeneration of the primary sensory neuron (amyloid neuritis, diabetes) it is distinct from these.

Heredity.—A glance at the genealogical table in Fig. 2 immediately reveals that the disease is transmitted as a Mendelian dominant. It has remained true to type except in two instances (Case 12 and Case 35), where tinnitus and vertigo had so far appeared as the only manifestations. One further case, and two doubtful cases are added since the record of Hicks in 1922. There is slight evidence of the " law of anticipation ", for whereas the second generation first developed the disease at the ages of 31, 33, and 30 years, the third generation showed onset at the ages of 15, 22, 32, 26, 24, and 35 years. The next generation was too young at the time of the examination in 1936 to have manifested the disease.

The families reported by others show a variety of types of inheritance, but in the larger families, such as that of Mulvey and Riely (1942) in which 11 members out of 37 in three generations were affected, the type of inheritance is clearly the same as in the family reported by Hicks and by me.

Further, I have seen three cases with identical clinical features but without family history. I present the sensory chart of one (Fig. 18), a young man of 24 years of age, who had attended Guy's

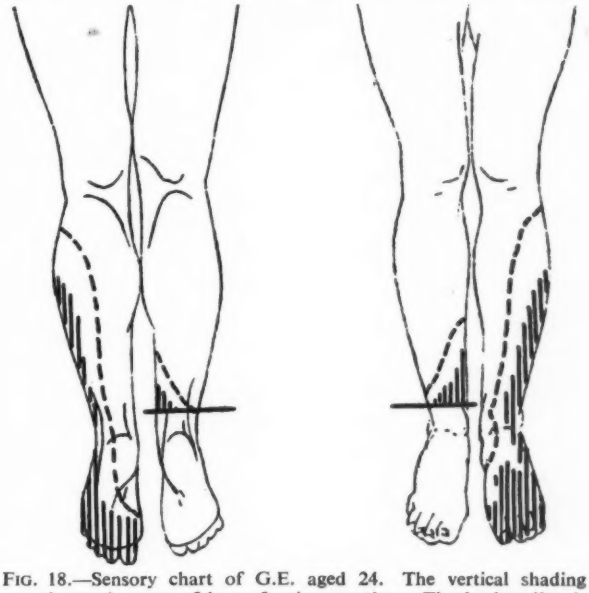


FIG. 18.—Sensory chart of G.E. aged 24. The vertical shading shows the area of loss of pain sensation. The broken line is the upper limit of hypalgesia. There was no loss of light touch sensation.

Hospital on a number of occasions since the age of about 17 years for perforating ulcer. He had had a complete neurological investigation, including serial lumbar puncture and radiographs of the spine, on several occasions, without evidence of any central pathology. The nerves were not thickened or tender, and there was no motor weakness or muscular atrophy. The ankle jerks were lost, the knee jerks present. There was no evidence of spina bifida, and no sphincter disorder. It was reported that there had been loss of sensation to pain in the right foot before it was amputated for severe trophic changes at the age of 18. The sensory changes shown in the chart were those found when he was last seen in 1939. There was no loss of sensation to touch. The radicular distribution of the dissociated sensory loss was obvious in the left foot. Trophic ulceration of the left great toe had been recurrent for four years.

It is therefore considered that sporadic cases of symmetrical neuritic perforating ulcer are not uncommon, and that the disease we have described can have sporadic, as well as hereditary and familial forms. The absence of motor paralysis or sphincter disturbance is a frequent, but not absolute, diagnostic feature. It will be noted that smallness of the musculature and mild sphincter disorder has been seen in some cases, including our own, but only very late in the course of the disease. Sym-

metrical bilateral paralysis of the fifth lumbar and first sacral roots, with perforating ulcers of the feet, reported by Egger and Chiray (1904), differs radically from the disease discussed here. In such cases the motor paralysis should lead to suspicion of prolapsed intervertebral disc, spinal bifida, or other cause of root lesion in spite of the absence of sphincteric paralysis. We have seen such a condition occurring as the residue of severe trauma to the cauda equina.

Conclusions

Post-mortem examination of a member of the family described by Hicks with "hereditary perforating ulcer of the foot" disclosed a primary degeneration of dorsal root ganglia. Deposits of amyloid were found in the most severely affected ganglia, and this is considered to be a secondary feature. The disease affected 11 of a family of 36, in three generations, and was characterized by dissociated disorder of sensation beginning in the feet, with progressive deafness. Two additional members suffered from tinnitus. The disorder was inherited as a simple Mendelian dominant. The greater loss of sensations of pain and temperature is a result of the radicular pattern of sensory loss. The disease has a sporadic and familial form as well as the hereditary type, and in these deafness is absent from the syndrome.

APPENDIX

HISTORY OF R. FAMILY

No. 1* Male
(*Affected*). Died 1874 at age of 51—account of relatives, ulcers in the feet, "rheumatism" (shooting pains), deafness. Arms not affected. Death certificate—"Embolism and gangrene" (Hicks).

No. 2 Male, William R.
(*Affected*). Brass finisher. Symptoms began in 1885 at age of 31. Repeated ulceration of both feet, amputation of second toe of right foot at age of 35, and part of left great toe at age of 44. Shooting pains in the limbs, thermal and pain loss noted in lower limbs, tendon reflexes absent, pupils reacted to light. Quite deaf in both ears for 10 years, before death in 1900, aged 46, of "tabes mesenterica" (Hicks). Recurrent diarrhoea for last 2 years (Dr. McArdle).

No. 3 Female, Mrs. C.
(*Affected*). In 1897 at age of 33 began to suffer from shooting pains in the legs, and from deafness at age of 39. At age of 41 perforating ulcers on the soles of both feet. Pupils reacted to light and accommodation, knee jerks lost, anaesthesia of lower legs. Blood Wassermann negative. Died at 46 of syncope (Hicks).

No. 4 Female, Mrs. Sarah Ann B.
(*Affected*). Disease began at age of 30. Suffered from ulcers of the feet, pains in feet and head, and deafness. Died in 1905 at age of 49. (Statements of family—Hicks.)

No. 5 Male, Robert R., aged 68.
(Unaffected). Alive and well in 1936. No ulceration, pain, or deafness. (Statements of family.)

No. 6 Female, Miss Elizabeth R.
(Unaffected). Alive and well in 1936, age 75. (Statements of family.)

No. 7 Female, Mrs. H., aged 80.
(Unaffected). Alive and well in 1936. (Statements of family.)

No. 8 Female, Mrs. Ethel C.
(*Affected*). Ulceration of sole of feet from age of 15. In 1919 knee jerks present, pupils reacted, no glycosuria. Blood Wassermann negative, no spinal bifida (Hicks). In 1921 wrote to Hicks stating she had now shooting pains, deafness, and more severe ulceration (Hicks). Died at age of 46—recurrent diarrhoea for the last few years. Had had amputation of foot. (Statement of relatives to Dr. McArdle.)

No. 9 Female, Lily R.
(Unaffected). Died, aged 24, of tuberculosis. Was married, no children.

No. 10 Female, Edith R.
(*Affected, our patient*). Died, aged 53. Onset first noticed ulceration of the feet in 1904 at the age of 22, knee and ankle jerks absent in 1921, pupils reacted to light, loss of pain and temperature sensation over lower parts of both legs, some deafness present (Hicks, August, 1921). Recurrent diarrhoea since 1933. For terminal state see full case report.

No. 11 Male, William R.
(Unaffected). Reported alive and well, aged 56 years, in 1936, and unaffected (information from family—Dr. McArdle).

No. 12 Female, Jane R.
(? Unaffected). Alive and well, aged 52, in 1936, suffering from chronic pulmonary

* Numbering according to Fig. 1.

tuberculosis. Has had intermittent tinnitus, mainly in left ear, for some months. No diarrhoea. (Seen by Dr. McArdle.)

No. 13 Male, Frank C.
(*Affected*). Traveller for a drug firm. Died, aged 48 years. Seen by Hicks in 1921 at age of 36 and found to have then a beginning perforating ulcer, and absence of ankle jerks. Knee jerks pressent, small patches of anaesthesia. A full report was obtained from Dr. Prausnitz of Ventnor, Isle of Wight, in 1936, stating ulceration of feet began at the age of 32 years and had been present off and on since. The knee jerks had remained present. Complete loss of sensation for pain in the feet, lower legs, and both hands. Had had bouts of diarrhoea. Very severe deafness had developed in the two years before 1936, with vertigo of Ménière type. Died in hospital in 1936; permission for necropsy refused.

No. 14 Male, Archibald C.
(*Affected*). Died, aged 39 years, a warehouseman, developed pulmonary tuberculosis while on active service in world war, subsequently a tram driver but gave this up in 1924 on account of ulceration in his foot. He lost the greater number of phalanges and some metatarsal bones by 1935, with a very large ulcer present. Deafness had slowly developed from ? 1930, and was not complete. He always refused examination. The pulmonary tuberculosis appeared to have healed in 1935. Urine reported normal (no albumin) in 1935. Died of bronchopneumonia following influenza in 1937. No necropsy. (Notes from Dr. Sylvester of Newport, Isle of Wight.)

No. 15 Female
(*Affected*). In 1915, at the age of 24, developed ulceration of the feet, admitted to hospital in 1920 (age 29) with ulceration of feet and discharge of pieces of bone from left foot. Pupils reacted normally. Arm reflexes present. Knee jerks brisk and equal. Ankle jerks and plantar responses not obtained. Slight analgesia and confusion between heat and cold in feet only. Tactile sensation normal. Wassermann reaction in blood doubtful, December 7, 1920, and negative, January 4, 1921. Occasional shooting pains over outer side of right thigh and in left leg at that time (account of Hicks). Patient died at age of 46 (account of relatives).

No. 16 Female
(? Unaffected). Age and whereabouts unknown.

Nos. 17, 18, 19. Died in infancy (family and Hicks).

No. 20 Female, Edith B.
(*Affected*). First had a corn in the left foot in 1920 at the age of 35, and intermittent pains in thighs, arms, and head, with beginning deafness, in 1921. At that time there was slight loss of thermal sensation in both feet, but none to pain or touch. Pupils reacted to light. No nystagmus. Knee jerks present but sluggish, ankle jerks, and plantar responses absent. Slight deafness present, no tinnitus. Aural surgeon reported findings analogous to primary cochlear degeneration (findings of Hicks). Reported still alive but severely affected in 1936 (information from family).

No. 21 Male
(? Unaffected). Not heard from for years.

No. 22 Male
(*Affected*). When last heard of in early 1920 was badly affected with ulceration of both feet, deafness, and tinnitus. No knowledge of him since (family information).

No. 23 Male
(Unaffected). Died of asthma in 1925 (information from family).

No. 24, 25, 26, 27, 28, 29 All married and none affected in 1936 (uncertain information from family).

No. 30 Male
(Unaffected). Aged 20 in 1936, backward and slow (reliable family information).

No. 31 Male
(Unaffected). Aged 24 years in 1936. (Reliable family information.)

No. 32, 33 Females. Unaffected. Aged 22 and 19 years, in 1936. (Reliable family information.)

No. 34 Male
(? *Affected*). Aged 21 years in 1936, radio repairer, attacks of vertigo for 3 years. No evidence of tuberculosis. No pains or paraesthesiae. Hearing normal. Pupils of moderate size and reacted briskly to light and accommodation. No wasting of muscles or weakness. No corns or ulcers. Arm jerks all sluggish. Knee jerks and ankle jerks sluggish, but all brisk with reinforcement. Plantar responses flexor. No loss of sensation to cotton wool, slight impairment to pin prick sensation below level of midcalf on both sides (examination by Dr. McArdle).

No. 35 Female, aged 12.
Unaffected in 1936 (reliable family information).

No. 36 Female, aged 6 years.
Reported healthy in 1936 (reliable family information).

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CALCIFICATION OF THE CORPUS STRIATUM AND DENTATE NUCLEI OCCURRING IN A FAMILY

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Dense symmetrical calcification of the corpus striatum is rare, but of some general interest for two reasons. First, in a significant number of the reported cases this apparently degenerative condition is closely linked with a metabolic disorder, hypoparathyroidism, which may be idiopathic, parathyroprivic, or of the variety in which the parathyroid glands are histologically normal but the body is unable to respond to parathormone (Albright's pseudohypoparathyroidism). Secondly, in no other degenerative disease limited to a neurophysiological system can the process be visualized radiologically. In contrast with the rare gross calcification under discussion, microscopically demonstrable calcification occurring on a basis of hyaline degeneration in and around the vessels in these regions is very common, and can, indeed, be found to a certain extent in normal brains. Such calcification formerly attracted much attention in certain inflammatory conditions, chorea, encephalitis lethargica, polio-encephalitis, and cerebral malaria ; in intoxications with carbon monoxide, nitrous oxide, and lead ; in degenerative conditions such as amaurotic idiocy and the progressive pigmentary pallidonigral degeneration of Hallervorden and Spatz ; and in certain metabolic and endocrine disorders (other than hypoparathyroidism) such as Addison's disease, cretinism, myxoedema, and severe pernicious anaemia. Calcification in the basal ganglia gross enough to be visible radiologically occurs in two main groups of conditions : in association with parathyroid insufficiency, as is now well known, and in certain rare familial instances. It is in the latter, of which the family reported below is the third in the literature, that the calcification attains its most florid form.

Case Report

Mrs. M.E., aged 60, was admitted to the Maida Vale Hospital for Nervous Diseases, London, under the care of Dr. P. H. Sandifer on January 17, 1949. She had had no previous illnesses of note, and on direct questioning there was no history of tetany or thyroid disorder. There was no family history of mental disturbance, epilepsy, or endocrine abnormality. The patient had had seven children. The first died in convulsion at three months, but the remaining six are well. Four years before admission it was noticed that the patient was becoming slower in her movements, and that her memory was failing. At about the same time she began to have brief attacks of vertigo, in one of which she fell forwards, cutting her head and leg ; none of these attacks was associated with loss of consciousness. One year before admission her gait became unsteady, and after a further eight months her legs were so weak and unsteady that she was unable to climb stairs without assistance. Such unsteadiness of the hands as occurred did not prevent her from helping with the cooking. Attacks of vertigo, unassociated with deafness or tinnitus, occurred three or four times daily and caused frequent falls. She also complained of feelings of numbness in the tips of the fingers and of tingling in the front of the thighs. She denied impairment of memory or concentration and considered her speech to be normal. She had occasional slight frontal headaches. She had never had any fits. No change in facial expression had been noticed. Her vision was good, as was her hearing. She admitted to unsteadiness of the hands and to clumsiness and stiffness of the legs ; sphincter control was normal. Her general health was good.

On examination she was seen to be a well-nourished woman with a high colour, and healthy hair, skin, and nails ; there was no thyroid enlargement, and general examination revealed nothing abnormal. Her blood pressure was 135/60. Mentally she was distinctly dull, with defective insight into her condition. Her memory for recent events was impaired ; she was unable to subtract serial sevens, but could retain six digits forwards, and reverse three. On the Wechsler-Bellevue verbal intelligence scale her I.Q. was 79 ; there was little evidence of deterioration, and it was felt unlikely that she had ever been of more than low average intelligence. There was no dysphasia, dyspraxia, or evidence of a specific defect of parietal lobe function. Speech was slow and slurred. The cranial nerves were normal except for a moderate deafness of the right ear due to

chronic otitis media ; in particular, vision was good ; the fields and fundi were normal and there was no cataract. The jaw-jerk was brisk, though not unduly so. There was no spontaneous tremor of the upper limbs : here tone was slightly increased and there was a little weakness of extension of the wrists. Discrete movements of the fingers were clumsy and there was a well-marked intention tremor, especially on the left. The tendon reflexes were brisk but equal ; there was no grasp reflex. Sensation was normal. The abdominal reflexes were present, though sluggish. The lower limbs exhibited a moderate degree of spasticity and weakness, especially on the right side, and there was marked incoordination in the heel-knee test. The deep reflexes were very brisk, but equal, and both plantar responses were extensor. Sensation was normal.

Investigations.—A radiograph of the skull showed a calvarium of normal size and shape ; the sellar region was normal. The pineal gland was faintly calcified and lay in the normal position. The caudate and lenticular nuclei on each side were heavily and symmetrically calcified, and the dentate nuclei were similarly calcified (Figs. 1a, 1b, and 2). Pneumoencephalography confirmed the position of the shadows (Figs. 3 and 4). The size of the ventricles was at the upper limit of normal, and the sulci of the frontal lobes were somewhat widened. The blood Wassermann and Kahn reactions were negative. The cerebrospinal fluid was under normal pressure, and normal in composition. The serum calcium level was normal on three occasions (9·3, 10·4, and 11 mg. per 100 ml.) and the serum phosphorus was 3·4 mg. per 100 ml. Alkaline and acid phosphatase values were normal (11·5 and 1·7 units respectively). The urine was normal. In tests for toxoplasma the complement fixation test was negative, and the cytoplasm-modifying antibody test positive 1/8.

Because there was a cholesteatomatous deposit in the attic a radical mastoidectomy was performed, after which the attacks of vertigo ceased.

Over the past two years the patient's condition has remained essentially unchanged, and the intracranial calcification has shown no increase in extent or density.

Skull radiographs of her elder daughter (L.N., aged 28) showed a mottled shadow on both sides in the position of the anterior part of the lenticular nucleus (Figs. 5a, 5b, and 6). In the case of the younger daughter (C.E., aged 21) only a very faint mottled shadow was visible (Figs. 7a, 7b). Both daughters enjoyed good health, were of average intelligence, and displayed no abnormal physical signs. Three of her four sons, aged 32, 27, and 26, were examined radiologically, and in none was any intracranial calcification visible.

Discussion

Much of the earlier work on calcification of the finer cerebral vessels in the divers conditions already mentioned was vitiated by a failure to recognize the occurrence of microscopical hyaline degeneration and calcification in the normal corpus striatum. Mallory (1896) showed that hyaline degeneration in the media and adventitia of small vessels, with subsequent deposition of calcium salts, occurs most frequently in the dentate nucleus, and that the droplets may fuse to form sheaths. The process affects the small arteries first, later the capillaries and veins. The principal difficulty, as later workers have realized, lies in determining at what stage the process becomes pathological. In 100 brains, affected by a wide variety of pathological conditions and of all ages, Hurst (1926) found microscopical deposits in the vessels of the globus pallidus, chiefly in the small vessels of the anterior half of the nucleus, though often with sparing of the extreme rostral tip. In 68% there were free-lying, so-called degenerative bodies staining blue-black with haematoxylin (termed by earlier writers chorea corpuscles, Flechsig's granules, or siderophile bodies, and by later workers pseudolime or pseudo-calcareous concrements) in the globus pallidus, and in 30% such bodies were also to be found in the putamen. They occurred solely in the putamen in only two cases. They were also to be observed more sparsely in the internal capsule, but they have not been reported in the red nucleus, reticular substance of the midbrain or pons, or in the inferior olives. He considered that their distribution could not be entirely correlated with that of iron, for they were never to be seen in the substantia nigra. The deposits themselves are highly refractile, often laminated, devoid of lipoid, glycogen and amyloid, and may be minute or sufficiently large to give a gritty feel to the knife. Ostertag's (1930) description of them accords well with that of other authors (Pick, 1902, 1903 ; Bassoe and Hassin, 1921; Weimann, 1922 ; Kasanin and Crank, 1935 ; Eaton, Camp, and Love, 1939 ; and Rand, Olsen, and Courville, 1943). They occur in three forms. They may lie free in the tissues, unrelated to the vascular system, varying in size from minute points to laminated spheres larger than a ganglion cell of the globus pallidus, or as " mulberry bodies " formed by the conglomeration of several spheres, these being encountered only in pathological conditions. Secondly, there may be deposited upon the outer side of capillaries innumerable globules, like strings of pearls, or, usually in pathological conditions, complete sheaths with or without obstruction of the lumen. Thirdly, dust-like particles and spherules may be deposited in the media, adventitia, and perivascular spaces ; in the early stages they do not destroy the media or occlude the lumen, but in advanced cases they become confluent and form large, irregular, branching, coral-like masses. The deposits do not occur within glial or nerve cells, and except where vessels have become occluded

FIG. 2

FIGS. 1a and 1b

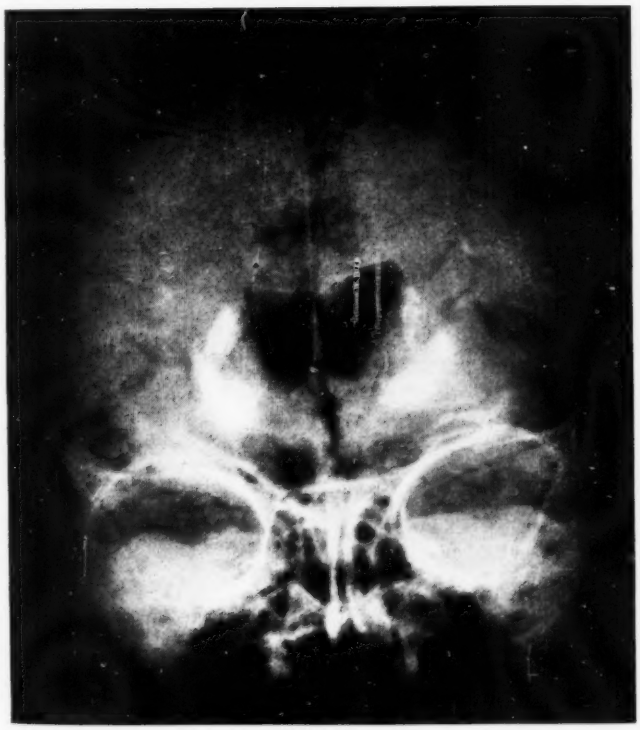


FIG. 3

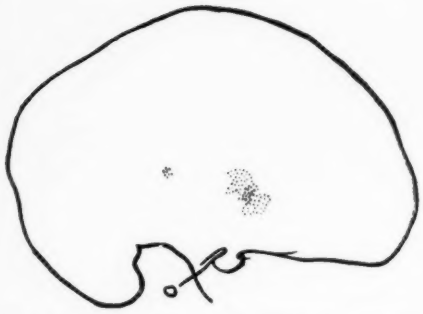
FIG. 4

FIGS. 1a AND 1b.—Dense calcification in the region of the corpus striatum and dentate nuclei in Case M.E.

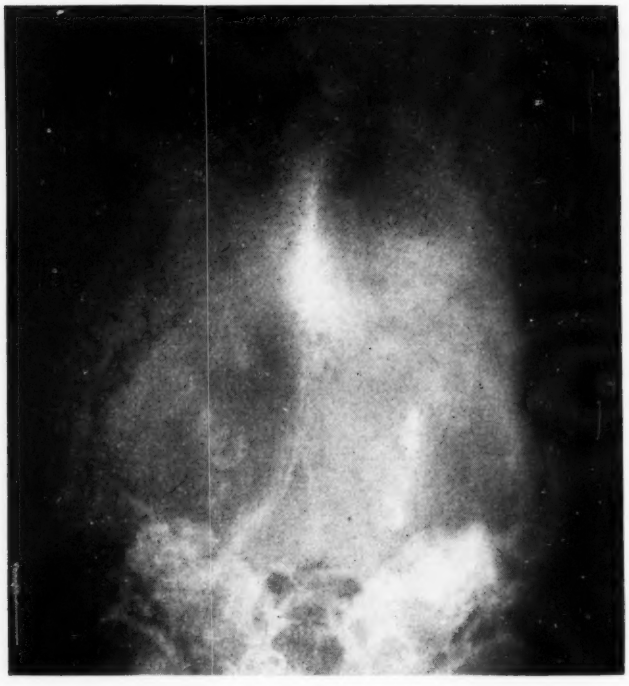
FIG. 2.—Half-axial view of skull. The dentate nuclei are clearly visible as sinuous shadows lying medially to the calcified lenticular nuclei.

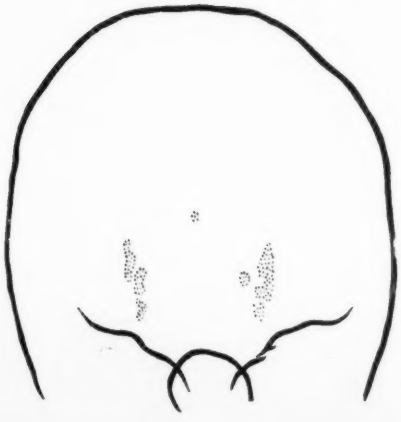
FIG. 3.—Pneumoencephalogram to show position of calcified shadows and excess of air in subarachnoid space.

FIG. 4.—Pneumoencephalogram ; reversed Townes projection.

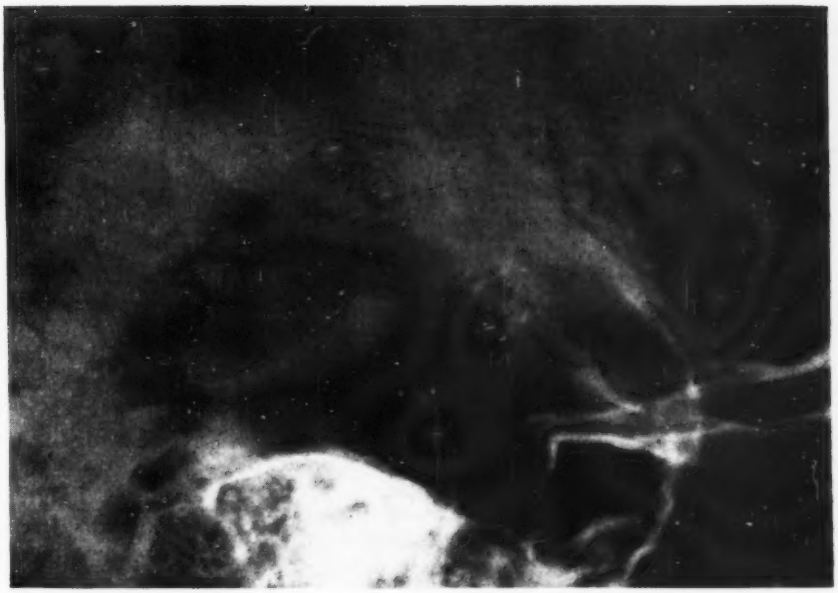


FIGS. 5a AND 5b.—Case L.N., elder daughter of M.E. . mottled calcification in the anterior part of the corpus striatum.





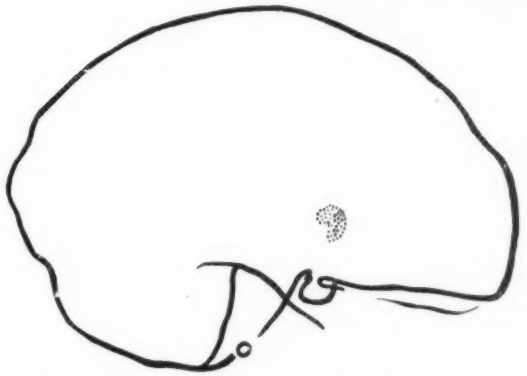
FIGS. 6a AND 6b.—Case L.N. : half-axial view : no calcification is visible in the dentate nuclei.



FIGS. 7a AND 7b.—Case C.E., younger daughter of M.E. Early calcification in the anterior part of the corpus striatum.

there is no reactive gliosis. The condition is certainly not related to medial sclerosis, for the earliest deposition is often adventitial, and the subintimal tissue is the last to be affected ; furthermore, in the cases reported the larger vessels at the base have always been normal. The groundwork of the deposits is a hyaline material staining as deeply with haematoxylin after decalcification as before. Debate as to whether these deposits contain iron or calcium or both has been considerable. Eaves (1926) showed that it is, in fact, calcium that is deposited in such abundance in the hyaline globules. In comparison with the amount of calcium, the quantity of iron present is small (Kasanin and Crank). Lowenthal (1948) summarized the evidence for the presence of hyaline, calcium, and iron in cases of symmetrical calcification of the corpus striatum reported up to that time.

The question arises, when may the concretions, present to some extent in the majority of brains, be regarded as abnormal? There appears to be no sharp division between the normal deposition of hyaline with its propensity for adsorbing calcium, and the abnormal as seen in the cases under discussion. The deposits in these cases are similar to those occurring in the neighbourhood of angiomatous malformations, in gliomas, at the edge of areas of necrosis, and in the familial calcifying epilepsy of Geyelin and Penfield (1929). It would appear that, so far as their appearance in the basal ganglia is concerned, these deposits may be regarded as abnormal only when they attain such a size as to become confluent and occlude vessels, causing local ischaemia and setting in train a progressive process itself tending to cause calcification.



Calcification of the Corpus Striatum and Hypoparathyroidism.—The occurrence of striking calcification in the corpus striatum in cases of tetany was noted by Pick (1902, 1903, 1905) ; Ostertag remarked upon the unusual density of the concretions in cretinism and mongolism. He suggested that in certain metabolic disorders excessive deposition of hyaline may occur in these regions because of some local metabolic peculiarity, with impairment of the blood supply of the ganglia and later parenchymatous damage. The particular association of radiologically demonstrable calcification in the basal ganglia with hypoparathyroidism was emphasized by Eaton and Haines (1939), Eaton, Camp, and Love (1939), Sevringhaus (1942), Mortell (1946), and Siglin, Eaton, Camp, and Haines (1947). Alexander and Tucker's (1949) case was one of the even rarer pseudo-hypoparathyroidism ; this patient, who exhibited the typical habitus described by Albright (Albright and Reifenstein, 1948), had suffered from epilepsy in adolescence ; in addition to subcutaneous calcinosis (which seems to be more common in pseudo-

hypoparathyroidism than in idiopathic hypoparathyroidism) he had calcification of the basal ganglia visible radiologically. At the age of 48 he developed a typical Parkinsonian tremor. The cases of Sprague, Haines, and Power (1945) with fits and calcinosis, and of Peterman and Garvey (1948) with fits, mental retardation, and behaviour disorder, were also examples of the condition in association with pseudohypoparathyroidism. The radiological features have been reviewed by Camp (1947, 1948). With regard to other endocrine disorders, a case of Addison's disease showing concretions histologically was reported by Ostertag. The coexistence of idiopathic hypoparathyroidism with adrenal insufficiency (not due to tuberculosis) has been commented on by Leonard (1946). She reported a child in whom the two conditions occurred together, with radiologically demonstrable calcification in the basal ganglia; unfortunately the necropsy findings in the brain were not published. Maleci and Bonomini's case (1948) had in childhood suffered from adiposogenital dystrophy, and there was also a doubtful history of late rickets; in view of the raised serum phosphorus level the case may well have been one of idiopathic hypoparathyroidism. Lowenthal (1948) attempted to define the relationship between striated calcification and parathyroid insufficiency. He found that of 32 cases collected from the literature 13 in all had evidence of parathyroid insufficiency. Of these, nine had clinical tetany (two with cataract as well), and two had cataract only; the remaining two had low serum calcium and raised phosphorus levels in the absence of rickets or renal failure, but displayed no signs of tetany. Most of these cases were examples of chronic idiopathic hypoparathyroidism; in three patients it followed measles, two of these being siblings. Striatal calcification is not peculiar to idiopathic hypoparathyroidism, for Scholz, quoted by Ostertag, reported a case following thyroidectomy, as did Siglin and others. It appears that a considerable time is required for the development of radiologically visible calcification after parathyroidectomy; Ostertag examined the brains of two cases of parathyroprivic tetany, dying six weeks and three months respectively after operation, and found no excess of concrements. Scholz's case came to necropsy 10 years after operation, while that of Siglin and others was radiographed 24 years after thyroidectomy.

To the 32 cases collected by Lowenthal may now, therefore, be added seven more examples with intracranial calcification: those reported by Eaves, Sevringhaus, Sprague, Mortell, Leonard, Peterman and Garvey, and Alexander and Tucker. Thus of 39 instances in the literature in which gross calcification was demonstrated either radiologically or at necropsy, no less than 19 had undoubted parathyroid insufficiency.

Familial Examples.—Fritzsche (1935) reported a family of three siblings, two of them females, in whom radiologically demonstrable calcification of the lenticular and dentate nuclei was associated with epilepsy, oligophrenia, and, in the most severely affected, muscular rigidity. There was no clinical evidence of tetany. He considered the condition to be a heredodegeneration, though the evidence in favour of this view is not conclusive. The possibility that the condition might have been the result of an infection which had affected the whole family was not considered. It should be mentioned that radiologically and clinically there is nothing to suggest that these were cases of toxoplasmosis. The only other example of familial calcification of the basal ganglia is that of Kasanin and Crank. Their case was one of mental deterioration with progressive rigidity; a sister had a mental and physical condition similar to that of the patient but was not, unfortunately, examined radiologically; seven siblings had died in childhood; five were still alive, and all were mentally retarded. The cases which are the subject of the present report appear to be the only ones in which a hereditary dyscrasia can be postulated with reasonable certainty.

Clinical Features.—In cases of hypoparathyroidism with calcification in the corpus striatum epilepsy and mental deterioration are the rule, both beginning in childhood or early adult life, except where removal of the glands is the cause. Episodes of confusion and psychotic behaviour may punctuate the course; finally coma may ensue. With the exception of bilateral nerve deafness, cranial nerve palsies are unusual, though diplopia and ptosis have been recorded. Paraesthesiae, symmetrical or otherwise, are common and early symptoms. Of the muscular disorders, cramps, and persistent pain and stiffness in the muscles and joints, are frequent. Carpopedal spasm and positive Chvostek's and Trousseau's signs are present in only half the cases. Of the ectodermal features, cataract is the most common, together with loss of hair and coarseness of the skin. The rarer syndromes connected with hypoparathyroidism, such as myosclerosis, sclerodermia with calcinosis, oesophageal spasm, and abdominal pain, have not been reported in cases showing intracranial calcification. Despite the density of the shadows in the basal ganglia, extrapyramidal symptoms and signs have in most cases been surprisingly scanty, though there is usually slowness and poverty of movement and facial expression.

In a few cases rigidity has been well marked, while one case, in whom the somatic features of pseudohypoparathyroidism were present in infancy, developed a Parkinsonian tremor at the age of 48. A slow, slurring dysarthria is common. Death occurs most often from intercurrent infection, but may result from a sudden attack of cyanosis with or without laryngeal spasm, or from raised intracranial pressure. The coexistence of epilepsy and papilloedema in cases of hypoparathyroidism without clinical tetany (Albrecht, 1924 ; Barr, MacBryde, and Sanders, 1938 ; Sutphin, Albright, and McCune, 1943 ; Leonard, 1946 ; Lyle, 1947 ; Berezin and Stein, 1948) is worth mentioning as it may lead to an erroneous diagnosis of cerebral tumour. The increased intracranial pressure has been attributed to cerebral oedema. Barr and others found that the calcium content of the cerebrospinal fluid of their case was normal, and suggested that the difference in concentration of calcium ions on the two sides of the haematoencephalic barrier may have been responsible for the raised intracranial pressure. Guillain, Bertrand, and Rouquès (1936) reported a case in which cramps, clinical tetany, petit mal, and generalized seizures were followed by obnubilation, bilateral papilloedema, and death. The serum calcium level was 9 mg. %, and the parathyroids were histologically normal. The globus pallidus and dentate nuclei exhibited in profusion the concrements already described. In addition there was in the white matter of one frontal lobe a minute focus of demyelination surrounded by filaments and round bodies strongly suggestive of a mycotic infection.

Cases not Associated with Hypoparathyroidism.—The clinical features of cases not associated with parathyroid insufficiency fall into two main groups. In the first, which includes the familial examples of Fritzsche and of Kasanin and Crank, mental retardation and epilepsy dating from childhood, with further deterioration in early adult life and a mixed pyramidal-extrapyramidal syndrome, have occurred. As a similar condition of oligophrenia with rigidity and epilepsy may be associated with cataract and deafness, it is not impossible that an early and transient hypoparathyroid state unrecognized in childhood, or passed off as epilepsy, may in certain susceptible individuals or families lead to progressive hyaline degeneration and calcification of vessels in the basal ganglia. A tendency to develop hypoparathyroidism may run in families ; it has already been mentioned that two of the three patients with hypoparathyroidism following measles were siblings, while of five cases of hypoparathyroidism (without intracranial calcification) following moniliasis three were siblings (Sutphin, Albright, and McCune, 1943 ; Albright and Reifenstein, 1948). Moreover, pseudohypoparathyroidism has a well marked familial tendency.

The second group is less uniform, comprising Eaton, Camp, and Love's Case 3 with thyrotoxicosis and no neurological features other than the brain calcification ; Case 4 with recurrent hemiplegia, and Case 5 with mental deterioration ; Bassoe and Hassin's patient with unilateral convulsions, intellectual impairment, dysphasia, hemiparesis, headache, and stupor leading to death, and their second case, the only one in which the calcification was confined to one side, with contralateral hemiplegia with athetoid movements ; in this girl the dentate nucleus was not calcified, and the cause may well have been a vascular accident in childhood. The subject of the present report showed intellectual impairment, slowness of movement, dysarthria, marked intention tremor in the upper limbs but no static tremor, and moderate spasticity with ataxia in the lower limbs. The affected daughters had no neurological disturbances, and there is no intracranial calcification in the sons. This incidence upon the female members of the family is interesting, and two of Fritzsche's three familial examples were females. Although in general dysfunction of the thyroid as well as of the parathyroid glands is more common in women than in men, amongst the cases of calcification of the corpus striatum reported in the literature males and females are equally represented. Whether the signs are predominantly cerebellar or predominantly extrapyramidal in the usual sense of the word presumably depends on whether the process occurs most markedly in the putamen and globus pallidus on the one hand or the dentate nucleus on the other.

Radiological Features.—There is no significant difference between the radiological features in the familial form and that associated with hypoparathyroidism. The calcification is clearly visible as multiple, dense, granular shadows, or in more advanced cases as striped or amorphous masses picking out clearly the caudate, lenticular, and dentate nuclei. The thalamus is always spared. The shadows are usually less marked in the dentate nuclei ; here they may be obscured by the petrous bones, but they can be shown up clearly in half-axial projections. In half the cases a few scattered flecks of calcification are visible in the centrum semiovale or in the white matter of the frontal lobes. Calcification is not seen in the meninges, cortex, or immediate subcortical white matter. The calvarium generally shows no abnormal features. Pneumo-encephalography confirmed the

position of the calcification in eight of the 17 radiologically demonstrable cases in the literature, and in case M.E. The ventricular system was normal in all except two ; in one of these there was moderate symmetrical dilatation of all the chambers, while in the other dilatation was limited to the third ventricle.

Aetiology.—Although the histopathological basis of the condition is clearly non-specific, the radiological features of all the reported cases are so similar that it is tempting to search for a common cause. The presence of hypoparathyroidism in 19 out of 39 examples is significant ; yet the great majority of cases of parathyroprivic tetany do not show intracranial calcification. However, nearly all the cases of hypoparathyroidism with intracranial calcification have been of the rare idiopathic variety or of the even more uncommon pseudohypoparathyroidism. It is conceivable therefore that some common factor may be responsible both for the so-called idiopathic hypoparathyroidism and for the excessive deposition of hyaline material around the vessels of the central grey matter, and that the metabolic disorder, with its tendency to supersaturation with regard to calcium and phosphorus as postulated by Albright and Reifenstein, results in a superabundant deposition of calcium in the hyaline material. In one example (without striatal calcification) in the literature (Winer, 1945) a diencephalic cause of parathyroid atrophy was suggested because of localized dilatation of the third ventricle ; a similar localized dilatation has been reported in one case with calcification. It is of some interest that the coexistence of parathyroid disturbance and striatal disease has been reported in two members of a family suffering from Wilson's disease of the " pseudosclerosis " type (Baltzan, 1936 ; Altschul and Brown, 1942). Of five siblings three had hepatolenticular degeneration, while one died young of cirrhosis. Of the former, one had hypocalcaemic tetany, but the parathyroid glands were not examined at necropsy ; while the other case had displayed no tetany, but at necropsy there was moderate atrophy of the parathyroid glands. As there was also some endarteritis of the parathyroid arteries it is difficult to be certain of the relationship of the parathyroid atrophy to the hepatolenticular degeneration.

The possibility that infection might be responsible for both the hyaline degeneration and the parathyroid atrophy has been entertained. One chronic infection at least, moniliasis, has been suspected of being a cause of parathyroid atrophy ; in such cases the infection precedes the metabolic disorder ; furthermore, moniliasis has also been found in two siblings with adrenal atrophy, one of whom probably had hypoparathyroidism as well (Talbot, Butler, and MacLachlan, 1943). While toxoplasmosis nearly always causes multiple small disseminated cortical and subcortical flakes and curvilinear streaks, in rare instances there may occur a dense granular or even confluent calcification of the basal ganglia (Sutton, 1951) with but few subcortical lesions. However, there is at present no evidence that this infection can disturb the function of the parathyroid glands, and in none of the cases of the condition under discussion has there been choroiditis or gross internal hydrocephalus. The strongest point against there being a single factor causing both the deposition of hyaline material in the brain and the hypoparathyroidism is the observation of calcification following accidental removal of the glands in two instances ; another point is the occurrence of intracranial calcification in cases of pseudohypoparathyroidism, which appears to bear no aetiological relation to the idiopathic form. Eaton and others, and Siglin and others concluded that the intracranial calcification is indeed the direct result of the parathyroid insufficiency, but left unexplained its rarity after accidental removal of the glands. The probable explanation of this is that tetany following removal of the glands is quickly and effectively treated, while idiopathic hypoparathyroidism, masquerading as epilepsy or progressive mental deterioration, may escape treatment for years. That a chronic infection is the primary cause of the intracranial deposits is improbable, because histologically the lesions show no inflammatory changes, and in an infective process it is reasonable to expect the lesions to be disseminated at random throughout the brain. In the cases under discussion, although there are often scattered flecks of calcification in the white matter close to the basal ganglia, the heaviest calcification falls with remarkable precision within the boundaries of a physiologically related system of nuclei.

Summary

A case is reported in which dense symmetrical calcification in the caudate, lenticular, and dentate nuclei, demonstrable radiologically, was associated with intellectual impairment, ataxia, and spasticity. There was no evidence of hypoparathyroidism. Both the patient's daughters, though free of neurological symptoms and signs, exhibited similar, though less well marked, radiological changes. Calcification was not detected in three of the patient's four sons.

In half the cases reported in the literature symmetrical calcification of the dentatopallidal system

has been associated with hypoparathyroidism, almost always of the idiopathic variety.

The occurrence of hyaline degeneration and gross calcification in these physiologically related nuclei leads to the supposition that their cells have a metabolic peculiarity capable of specific derangement by a raised level of serum phosphorus or a low level of serum calcium. It is possible that a transient parathyroid insufficiency may cause a permanent, or even progressive, hyaline degeneration in and about the vessels of the basal ganglia.

There is some evidence that the process may result from certain rare chronic infections, and that such infections may affect predisposed families.

There is no radiological difference between cases with and without hypoparathyroidism, though in the latter the calcification tends to be more dense.

I am indebted to Dr. P. H. Sandifer for permission to report these cases, and for his encouragement and advice; to Dr. J. G. Greenfield for his helpful criticism; to Dr. J. W. D. Bull for the radiological reports; and to Dr. I. A. B. Cathie for performing the tests for toxoplasma.

Lateral and half-axial views of the skull of case M.E. have been published in "Modern Trends in Neurology", edited by Dr. Anthony Feiling (London, 1951), in the chapter on diagnostic neuroradiology by Dr. J. W. D. Bull.

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THE CENTRIPETAL PATHWAY FROM THE BLADDER AND URETHRA WITHIN THE SPINAL CORD

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While clinical and experimental facts about lesions of the spinal cord and the functioning of the bladder have been collected for more than 50 years, knowledge remains inadequate concerning the afferent pathway from the bladder within the central nervous system of man. In 1906, von Frankl-Hochwart and Zuckerkandl wrote in their monograph on neurological disorders of the bladder: "Sehr gering ist noch unser Wissen über die spinalen Leitungsbahnen; am Menschen ist man nie über unbeweisbare Hypothesen hinausgekommen". They also stated specifically that nothing was known about the ascending tracts concerned with conduction from the bladder. In 1919, Müller still found it necessary to write: "Über die Bahnen im Rückenmark, durch welche die Empfindungen von den Blasenkontraktionen zentralwärts geleitet werden, und über die Stelle im Gehirn, wohin diese projeziert werden, sind wir noch völlig im Unklaren". In 1939, Bing and Haymaker wrote: "The pathways which the afferent fibres follow to reach the conscious level are not known".

Barrington investigated the problems of localization of the central nervous pathways by means of experimental lesions in animals. In 1925, he reported the results that he had obtained by making lesions in the midbrain of the cat; he found that "destruction of the midbrain from the ventral half of the side of the posterior end of the aqueduct outwards to just beyond the mesencephalic root of the fifth nerve is followed when the lesion is bilateral by a permanent loss of consciousness of wanting to micturate or defaecate". In 1933, he reported further work, showing the position of the afferent pathway in the spinal cord of the cat. He concluded that the whole or a large part of the centripetal pathway must lie in a superficial area in the posterior part of the lateral columns, not reaching as far posteriorly as to abut against the root entry zones. This region is shown in Fig. 1 (a reproduction of Fig. 4 of Barrington's paper).

Fig. 1.—Diagram of transverse section of spinal cord of cat. The area within which the centripetal bladder pathway lies is shown by stippling.

Among the many clinical papers which are concerned with the effects of lesions of the central nervous system on bladder function, we know of only one which considers the afferent tract, that by McMichael (1945), who reported the case of a patient who had lost sensation of bladder fullness. Sections of the spinal cord showed an area of degeneration anterior to the posterior horns in the lateral columns. This area could not be traced cranial to the thoracic region.

It is the purpose of this paper to present evidence concerning the location within the human spinal cord of the centripetal pathways (1) from the bladder, conveying impulses subserving (*a*) the desire to micturate, (*b*) pain; and (2) from the urethra, conveying impulses subserving (*a*) touch, (*b*) pain, (*c*) temperature, and (*d*) proprioception from the muscles working in association with the urethra.

Material

The material consists of 27 patients with lesions of one or both antero-lateral columns of the spinal cord, and of three control patients, in whom these regions were intact. Of the 27 patients, 24 had the operation of antero-lateral cordotomy performed for pain associated with cancer; one had this operation performed for the pain of tuberculous cystitis; and two patients had arterial thromboses, one of the anterior spinal artery, and one of a posterior inferior cerebellar artery. The patients of the control group suffered from amyotrophic lateral sclerosis, subacute combined degeneration of the cord, and from Friedreich's ataxia. Histological preparations have been made of 18 of the first group, and of all of the control groups.

The operations of spino-thalamic cordotomy were carried out for the relief of pain. The area of cord transected, although planned to give the maximum relief of pain, was varied to some extent from patient to patient. Seventeen of the patients were under the care of Mr. McKissock or in the wards of the Research Unit; they were fully investigated on several occasions before and after operation. Through the kindness of other neurosurgeons, other patients have been made available to us; these cases have been investigated only after operation. As the surgical interference has been undertaken for the relief of pain associated with cancer, the survival period has been relatively short; therefore it has been possible to determine histologically the extent of the incision in the cord and the resulting ascending and descending degeneration.

Investigation

Clinical.—The investigation falls into two sections, clinical and histological.

Bladder Sensation.—The main clinical evidence is based on day to day observation of the patient. Special investigations often added little to what was obvious on clinical observation. For example, if a patient is lying in bed with the bladder distended so that it can be felt as a dome between the pubic crest and the umbilicus, and the patient is quite unaware of this state of extreme distension, it can be concluded without further investigations that the patient has lost the sensation of needing to micturate and that of pain from over-distension of the bladder. Wherever possible, however, conclusions drawn from these observations were confirmed by observing what occurred under the controlled conditions of cystometrography.

Immediately after the operation of spino-thalamic cordotomy, which, when performed bilaterally, caused retention of urine, the bladder was allowed to become distended in order to find out what sensations were experienced; catheterization was then performed to relieve this distension. Cystometrography was carried out before and after operation. It was possible in this way to record the conditions of pressure and fluid content which gave rise to any form of vesical sensation, and to compare records made before and after the operation. The patients were asked to report any sensations they experienced. The evidence thus depends entirely on the subjective experience of the patient.

The method of cystometrography employed was designed to imitate as closely as possible the normal filling of the bladder. After the bladder had been emptied by catheterization, fluid—a warmed solution of proflavine sulphate, 1 in 10,000 in normal saline—was allowed to flow through a catheter into the bladder, at a rate of one to two drops a second. The pressure at which the fluid entered the bladder was the same as that which the bladder exerted on its contents.

A drawing of the apparatus is shown in Fig. 2. The proflavine solution, stored in a graduated reservoir, passed through a drip-bulb, the rate of flow being adjusted by a screw-clip. The drip-tube was connected by three channels; first to the catheter, which had previously been fixed in the bladder, secondly to a manometer, consisting of an upright glass tube, open to the air, and thirdly to a hollow C-spring, attached to the end of which was an ink-writer. The pressure in the bladder at any given moment could be read from the height of the fluid in the manometer. While the record was being made, the patient was invited to say what sensations, if any, were experienced. It will be noted that the amount introduced into the bladder from the reservoir was not necessarily the same as the fluid contents of the bladder, because the kidneys were secreting urine throughout the investigation. The total fluid content was obtainable only at the end of the investigation, when the total contents withdrawn by catheter were measured.

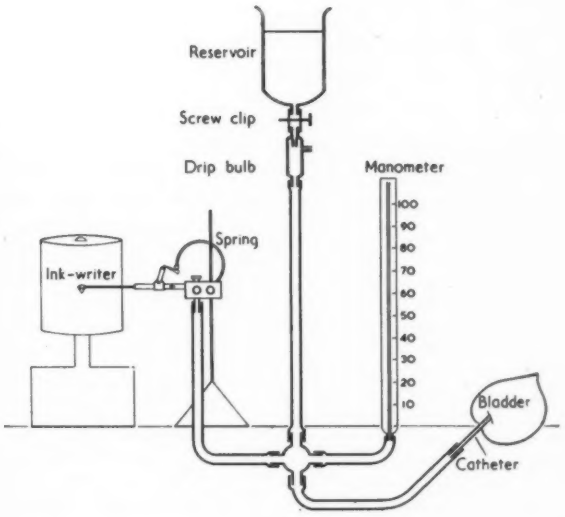


FIG. 2

Pain sensibility in the bladder was investigated in various ways. During cystoscopy, which was performed before and after operation, attempts were made to induce pain by indenting and stretching the neck of the bladder, the trigone, the bladder walls, and the ureteric orifices. The loss of painful sensation, when the bladder

was allowed to become distended after the bilateral operation, was taken to indicate that the pathway subserving the pain of bladder distension had been divided. In some patients, the spino-thalamic cordotomy had been performed for a painful condition of the bladder ; if the operation relieved this pain, then the pathway subserving pain in the bladder must have been divided. In other patients, who have had the operation of bilateral cordotomy, a condition of the bladder has been found post-mortem that is known to be painful ; such are inflammation of the viscus and ulceration. As there were no complaints of pain during life, it was concluded that the operation cut the tracts conveying impulses interpreted as pain. It is therefore possible to determine by analysis the centripetal pathway subserving pain caused by a variety of bladder conditions.

Urethral Sensation.—From the normal urethra impulses are transmitted subserving sensations of touch, of warmth and cold, and of pain. In addition, one of the main sources of sensation associated with micturition is proprioception from the muscles that act in association with opening and closing of the sphincter. The sensations of pain, touch, and of forceful opening of the sphincter by a catheter or cystoscope were noted before and after operation. The patients were also asked to observe what they felt when they passed urine voluntarily or involuntarily.

As it is not yet definitely known whether the bladder mucosa is sensitive to thermal stimuli, and as the urethral mucosa definitely is sensitive to such stimuli, no attempt was made here to differentiate the site of origin of the thermal sensations experienced. Proflavine solution at various temperatures was introduced into the bladder through a urethral catheter before and after operation. The patient was asked to comment on the sensations experienced.

Histological.—Fixation of the spinal cord was initiated as soon after death as possible. In the majority of cases the cord was fixed *in situ* ; 20% formol saline was injected into the cisterna magna, while cerebrospinal fluid was drained by lumbar puncture ; after a few hours the brain and cord were removed, and the necropsy completed. Fixation of the brain and cord in 20% formol saline was continued for 10 to 18 days, and the cord was then divided into segments. To demonstrate degenerated pathways, the techniques used were the Swank Davenport modification of the Marchi method, the Kulchitsky modification of the Weigert Pal method, and Gros' silver method. The blocks were embedded in celloidin.

Sections were taken at several levels of each segment of the cord, and in areas of special interest, serial sections were prepared. In the majority of cases the modified Marchi method was found to give satisfactory results, even when the interval between operation and death was about a year (Smith, 1951). Silver and Weigert Pal preparations were used to confirm the findings shown by Marchi staining. It was considered necessary to use the silver method in order to show destruction of axis cylinders, for the myelin stains may not demonstrate the absence of small, poorly myelinated fibres.

Clinical Evidence

In normal subjects, the vesical pressure at which sensations are experienced varies considerably from time to time, and from subject to subject. Also, the sensations experienced are related to the rate of filling, and to the rate of change of pressure. However, in all normal subjects, when the bladder contains a certain quantity of fluid, a stage is reached when there is a definite desire to micturate. In the present investigation, 20 healthy men and women were examined by the method of cystometrography described. An average of the figures from these subjects showed that there was a definite, insistent desire to micturate when the bladder contained 340 ml. of fluid at a pressure of 14 cm. of water.

The clinical evidence is presented in a condensed form as Table I. Those cases marked with an asterisk are mentioned in further detail.

Case 9.—Immediately following the second stage of a bilateral sympathectomy this patient developed a thrombosis of the anterior spinal artery. This caused complete analgesia throughout the right side below the second lumbar dermatome and throughout the left side below the third lumbar dermatome. There was retention of urine ; the patient had no normal desire to micturate, and no pain with the retention. Eventually she got a feeling whenever her bladder was distended, which she described as follows : " My tummy feels uncomfortable ; it is a feeling of wind really ; I cannot tell which it is ; it is not the normal feeling of having to empty the bladder, only an uncomfortable feeling in the tummy ". She could feel a catheter being passed, but it was entirely painless. Often, when bed-pans were being taken round the ward, she would get a normal feeling of needing to micturate, but it lasted only a minute or two, and would be unrelated to the state of distension of her own bladder.

Case 10.—This case showed much degeneration of all afferent pathways ; it is included in this series, as it is adequate for supplementary evidence, and because this patient, a man of 21, gave such good descriptions of his sensations. Following the operation of bilateral cordotomy, pain sense was diminished below the eleventh thoracic dermatome on the right, and absent throughout the left below the tenth thoracic dermatome. There was retention of urine, but the patient was unaware of this. He soon found, however, that he could tell when his bladder was full, as he got a sensation which he described as follows : " When my belly feels very full, as though I have eaten a lot, I know I have to empty my bladder ". The normal sensation that his bladder needed emptying had gone. This patient later explained that the feeling of abdominal fullness which he got when his bladder was full, seemed to him to be unrelated to his bladder ; it seemed to occur vaguely and generally within his abdomen ; sometimes this sensation also occurred when his abdomen was full of wind or his rectum full of faeces ; in itself the sensation was non-

specific ; he learnt by experience that it usually meant that his bladder needed emptying. When he was being catheterized, he felt nothing until the tip of the catheter passed the membranous urethra, when he explained that he had merely the feeling of the presence of something in that region ; it was a painless sensation. Before operation catheterization had been painful, and had left a soreness afterwards.

When micturition became automatic he would get, just before it began, a tingling and itching in the penis. This sensation could also be induced by giving 0·25 mg. of carbaminoyl choline (carbachol), which would cause urine to be voided.

Case 18.—This patient before bilateral cordotomy had such terrible pain every time he micturated that often he had to be given " trilene " by inhalation. His bladder was shrunken, and he had to micturate every five or 10 minutes. A bilateral antero-lateral cordotomy was performed by Mr. O'Connell under local anaesthesia. By the time the cord was exposed, the patient had a most urgent desire to micturate and much pain in the bladder. When the cord had been bilaterally incised, the pain and the desire to micturate were simultaneously relieved. After the operation, which caused analgesia below the fourth thoracic dermatome, the patient eventually had to empty his bladder only once every hour. He was able to do this while carrying on a conversation, a state of affairs quite unlike that which had prevailed before the cordotomy.

Case 19.—Following bilateral cordotomy there was complete analgesia throughout the body below the fourth thoracic dermatome. On the evening of the day of operation, the patient was catheterized on account of retention of urine : he noted that he felt the passage of the catheter, although it was painless, whereas before operation it had been so painful that it had almost to be given up. On the next day, he was found with his bladder full and distended, so that it could be felt above the pubic crest. He was moaning on account of the pain of it. He said that the bladder felt full, although the sensation was a new one, and not the normal feeling of urgently needing to micturate ; it differed in that it was not felt in the penis or perineum, but was situated only in the lower abdomen, above the pubic crest. When his distended bladder was pressed on through the abdominal wall, the pain was increased. It was found that he got no pain on having his testicles squeezed, his pubic hair vigorously pulled, and that pinprick on his penis and scrotum was felt only as touch. This lower abdominal pain was associated with bilateral frontal headache ; both pain and headache went when the bladder was emptied. He gradually developed more sensation in the urethra. When the catheter was passed, he got a tickle in the penis ; sometimes he got a pricking or irritation at the meatus ; as it passed along the membranous urethra he got a desire to micturate, and this feeling always became intense when the tip of the catheter reached the membranous part. Then he found that whenever micturition was about to begin, he would get the same pricking feeling in the penis ; he also got it when he strained to micturate, and also if too big a catheter reached the posterior urethra. He had no normal feeling that his bladder was full and no normal desire to micturate ; when it was very full, he sometimes got a pricking sensation above the pubic crest, which would go away as urine was let out. Four weeks after the operation, he again had some pain in his bladder and in the tip of the penis ; the bladder contained 640 ml. of urine. He stated that this pain was the normal sensation one has when one needs urgently to micturate.

Case 20.—Following unilateral cordotomy there was analgesia throughout the right side of the body below the fifth thoracic dermatome. There was for a few days after the operation " not a pain, well, yes—a pain, but only slight " immediately above the pubis and just to the left of the midline, when he needed to micturate. He then found that he had the feeling of needing to micturate only on the left side, the side of the body that was normally innervated. Later, he felt it mainly on the left, and eventually he noticed no laterality in the sensation, having a normal sensation underlying the desire to micturate.

Case 23.—Following deep *x*-ray treatment, the patient got severe pain in the left thigh and knee ; he also got a strange feeling of warmth running down the left thigh when he micturated ; this was accompanied by frequency of micturition. During cystoscopy, the following observations were made. As the cystoscope reached the posterior urethra, he had a desire to micturate ; he got the same desire when this part of the urethra was stretched. The bladder was filled at a pressure of 50 cm., and when it contained 600 ml. he got an urgent need to micturate. Some of the fluid was released ; then rubbing of the trigone with the cystoscope again brought on the desire to micturate. A ureteric catheter was then put into the right ureter ; this gave him the feeling of a pricking on the right side of the penis ; as the ureteric orifice was stretched, the pricking feeling became a continuous pain ; as the catheter was pushed up the ureter, it felt as though " you are pushing in a tender place on the right ". On the left half of the bladder, there were many telangiectases, doubtless due to radiotherapy ; the slightest touch over these with the tip of the ureteric catheter caused severe pain, felt either on the left or just to the left of the midline or centrally. The left side of the bladder was so tender, that search for the ureteric orifice had to be given up.

Following unilateral cordotomy there was total analgesia throughout the left side below the twelfth thoracic dermatome. Cystoscopy was repeated three weeks after operation. The bladder was filled at a pressure of 50 cm. ; when 700 ml. had been put in, the patient got an urgent desire to micturate, only on the right side. The ureteric catheter was pressed into the lateral walls ; nothing was felt on the left, a slight pain was felt on the right. The telangiectases, so sensitive before the operation, were rubbed vigorously (they occurred only on the left side of the bladder) ; nothing was felt. Both ureteric orifices were then stretched as much as possible by means of the ureteric catheter ; nothing was felt on the left ; on the right, penetration caused a slight feeling of pressure, stretching caused a

TABLE

OBSERVATIONS ON BLADDER AND URETHRAL SENSATION MADE ON 27 PATIENTS WITH LESIO

Case No.	Sex	Plate and Fig. Nos.	Diagnosis	Lesion in Cord			Survival in Days	Necropsy	Dermatome below which Analgesia is Present		Sensation Underlying Desire to Micturate			Bladder Pain		
				Bilateral Cordotomy	Unilateral Cordotomy	Other Lesion			Right	Left	Absent	Present	Unilateral	Present on Extreme Distension after Occurrence of Spinal Lesion	Due to Pathological Condition of Bladder: Present before Lesion	Due to Pathological Condition of Bladder: Present after Lesion
1	F	Plate I Fig. 3	Carcinoma of cervix	+	–	–	66	+	6th Th.	9th Th.	+	–	–	–	+	–
2	M		Carcinoma of prostate	+	–	–	75	+	11th Th.	7th Th.	+	–	–	–	–	–
3	F		Carcinoma of cervix	+	–	–	203	+	10th Th.	10th Th.	+	–	–	–	–	–
4	M		Carcinoma of pancreas	+	–	–	80	+	6th Th.	6th Th.	+	–	–	–	–	–
5	F	Plate I Fig. 4	Carcinoma of cervix	+	–	–	230	+	12th Th.	12th Th.	+	–	–	–	–	–
6	F	Plate I Fig. 5	Carcinoma of cervix	+	–	–	42	+	9th Th.	5th L.	+	–	–	–	–	–
7	F		Carcinoma of cervix	+	–	–	24	+	10th Th.	8th Th.	+	–	–	–	+	–
8	F		Carcinoma of colon	+	–	–	23	+	6th Th.	10th Th.	+	–	–	–	–	–
9*	F		Anterior spinal artery thrombosis	–	–	Anterior two thirds of cord	231	+	2nd L.	3rd L.	+	–	–	–	–	–
10*	M	Plate II Fig. 6	Chondrosarcoma of ilium	+	–	–	141	+	11th Th.	10th Th.	+	–	–	–	–	–
11	F		Carcinoma of rectum	+	–	–	240	+	2nd L.	9th Th.	+	–	–	–	–	–
12	F		Carcinoma of cervix	+	–	–	118	+	5th Th.	5th Th.	+	–	–	–	–	–
13	M	Plate II Fig. 7	Secondary carcinoma in ischium. Primary never found	+	–	–	109	+	12th Th.	12th Th.	+	–	–	–	–	–
14	F		Melanoma	+	–	–	162	+	12th Th.	12th Th.	+	–	–	–	–	–
15	F		Carcinoma of vagina	+	–	–	75	–	9th Th.	10th Th.	+	–	–	–	–	–
16	F		Carcinoma of cervix	+	–	–	240	–	10th Th.	10th Th.	+	–	–	–	–	–
17	F		Carcinoma of cervix	+	–	–	165	–	1st. S.	9th Th.	+	–	–	–	+	–

* Cases marked with an asterisk are given in text in further detail.

LESIONS OF THE ANTERO-LATERAL COLUMNS AND THREE PATIENTS WITHOUT SUCH LESIONS

Presence of Abnormal Sensation Related to Bladder Fullness	Sensation on Catheterization	Thermal Sensation	Comments
Frontal headache	Felt catheter—no pain		Necropsy examination showed in the middle of the trigone a sloughing ulcer 1·5 cm. diameter, the floor of which was formed by a thin membrane separating it from the anterior wall of the carcinomatous cervix. Mucosa, particularly of trigone, reddish purple.
Vague feeling of abdominal fullness	Felt catheter pass—no pain		Necropsy examination showed that the carcinoma of the prostate had invaded the bladder; the mucosa was grossly infected, but not ulcerated.
An accentuation of paraesthesiae of vibration in lower limbs	Unpleasant irritation in urethra and vagina; throbbing pulsating sensation in urethra		Unpleasant irritation was felt in vagina and deep in pelvis whenever she had a vaginal douche, or if she was catheterized, or if her rectum was very distended. The feeling was so diffuse and vague that it gave her no indication which of these stimuli was causing it. Necropsy examination showed that the bladder was grossly infected.
An ache across lower abdomen	With eyes shut, he felt glans being cleaned, catheter introduced into meatus; nothing else; no pain		Necropsy examination showed a normal bladder
	Felt catheter—no pain		Necropsy examination showed that the carcinoma had invaded the bladder
			Necropsy examination showed that the carcinoma had invaded the bladder
—	Felt nothing		Necropsy examination showed that the carcinoma had invaded the bladder
Vague feeling of abdominal distension	Catheter felt only on left side of urethra (analgesia being incomplete on the left)		The feeling of abdominal distension was so vague that she never knew whether its cause was flatus or a distended bladder
See text	Felt catheter pass—no pain	—	
See text	See text		
"A sort of warm feeling" in lower abdomen and perineum	Catheter scarcely felt—no pain	—	Necropsy examination showed that the carcinoma surrounded the neck of the bladder and had invaded the vesical muscle
Feelings in lower abdomen	Felt nothing		
"It feels heavy" in lower abdomen	Catheter felt—no pain. 12 days after operation he got a slight desire to micturate when the tip of the catheter reached the posterior urethra		Necropsy examination showed that the carcinoma had invaded the bladder
She felt she could not get a full breath as bladder was filled. When bladder was very full, abdomen felt distended.	Felt catheter—no pain	—	One month after operation she found that she knew immediately before automatic micturition that the act was about to occur. She was not sure whether this was a normal sensation underlying the desire to micturate or not. When the bladder was caused to contract reflexly, by suddenly raising the pressure, she got a sensation that she was passing urine, or was about to pass it, or that she wanted to pass it.
"My stomach feels full"	Felt nothing		
Slight tingling in bladder region	Felt nothing		
—	Before operation severe pain on having any instrument passed into urethra. After operation this pain could not be induced. Could feel urine passing		Cystoscopic examination showed that the carcinoma had invaded the bladder, in the neighbourhood of the ureters

[*Continued overleaf*

TABLE I—(*Conti*

Case No.	Sex	Plate and Fig. Nos.	Diagnosis	Lesion in Cord			Survival in Days	Necropsy	Dermatome below which Analgesia is Present		Sensation Underlying Desire to Micturate			Bladder Pain		
				Bilateral Cordotomy	Unilateral Cordotomy	Other Lesion			Right	Left	Absent	Present	Unilateral	Present on Extreme Distension after Occurrence of Spinal Lesion	Due to Pathological Condition of Bladder	
															Present before Lesion	Present after Lesion
18*	M		Tuberculous cystitis	+	−	−	<4 years	−	4th Th.	4th Th.	+	−	−	−	+	−
19*	M	Plate II Fig. 8	Carcinoma of bronchus	+	−	−	123	+	4th Th.	4th Th.	+	−	−	+	−	−
20*	M	Plate III Fig. 9	Carcinoma of bronchus	−	+	−	110	+	5th Th.	−	−	+	+	+	−	−
21	M	Plate III Fig. 10	Chondro-sarcoma of ilium	+	−	−	159	+	9th Th.	5th Th.	−	+	−	−	−	−
22	M	Plate III Fig. 11	Carcinoma of rectum	+	−	−	154	+	−	1st S.	−	+	−	+	−	−
23*	M		Carcinoma of colon	−	+	−	358	−	−	12th Th.	−	+	+	+	+	−
24*	M		Posterior inferior cerebellar artery thrombosis	−	−	See text	<180	−	Below mandibular division of N.V.	−	−	+	+			
25	F		Carcinoma of vagina	+	−	−	65	−	1st S.	9th Th.	−	−	+	+	−	−
26	M		Osteoarthritis of hip-joint	−	+	−	<5 years	−	−	6th Th.	−	+	−	+	−	−
27	F		Painful amputation stump	−	+	−	<2 years	−	6th Th.	−	−	+	−	+	−	−
28	M	Plate IV Fig. 12	Motor neuron disease	−	−	Degeneration of pyramidal tract	<2 years	+	−	−	−	+	−	+	−	−
29	F	Plate IV Fig. 13	Subacute combined degeneration of the cord	−	−	Posterior columns	1 year	+	−	−	−	+	−	+	−	−
30	F	Plate IV Fig. 14	Friedreich's ataxia	−	−	Pyramidal tract; posterior columns; spino-cerebellar tracts	29 years	+	−	−	−	+	−	+	−	−

* Cases marked with an asterisk are given in text in further detail.

(*Continued*)

Presence of Abnormal Sensation Related to Bladder Fullness	Sensation on Catheterization	Thermal Sensation	Comments
—	—		
Vague feeling of abdominal fullness and pricking in penis	Pricking and irritation at meatus ; tickle in penis		
—	Catheter not felt on right		
—	Catheter hurt less than before operation		Although this was a bilateral cordotomy, the incision on the left side of the cord was made purposely superficial and somewhat anterior. The analgesia was typical of division of one spino-thalamic tract. After the first 10 days, the sensation underlying the desire to micturate was normal.
—	—		Necropsy examination showed a normal bladder, not invaded by carcinoma.
—	Catheter not felt on left	Absent on analgesic side	
—	Catheter not felt on right	Absent on analgesic side	
Uncomfortable aching above pubis	Catheter not felt on left		The analgesia was total only unilaterally : on the right side of the body there was only diminution of pain below the first sacral dermatome. By the time the sensation of pain recovered to the state of diminution of pain, the patient had regained the sensation underlying the desire to micturate ; this was felt only on the side of the body that was hypoalgesic. This sensation was diminished, as shown by the fact that 840 ml. of urine in the bladder, distending it so that it was felt as a dome above the pubis, caused her little distress, the little sensation she experienced was felt only on the right.
—			The patient noticed no change in the desire to micturate until his bladder became over-distended ; then he realized that he had this sensation only unilaterally.
—			The patient had no change in the sensation of needing to micturate under normal circumstances, but as soon as the desire became at all urgent, she noticed that she felt it more on the side of the body with normal sensation.
—			Case included as control
—			Case included as control
—			Case included as control

pain felt on the right. Pressure with the cystoscope on the trigone caused a severe urge to micturate, felt only on the right; pressure on the bladder neck in the midline caused a feeling of pressure on the right side of the pubic crest. The ureteric catheter was then pushed hard in the midline into the wall of the bladder at the junction of the posterior wall and the dome; this caused no sensation on the left, and a moderate pain just to the right of the midline of the pubic crest. Strong pressure was then applied with the cystoscope on the left side of the bladder neck; this caused no sensation on the left, but a sharp pain on the right, of the kind that accompanies an urgent need to micturate. It will be realized that actually pressure in this region cannot be made unilaterally, so that pressure on the left must have pulled on and distorted the right half of the bladder neck and posterior urethra. Two days later cystometrography was carried out. The catheter was felt only on the right. All the sensation that he needed to micturate, and finally, the urgent desire to micturate, were felt only on the right. When it was pointed out to the patient that it was difficult to imagine such a sensation, he insisted that it was so, saying that he felt the full state of his bladder on the right side of his penis, on the right side of his perineum, and generally in the pubic region on the right. When 675 ml. of fluid had been run in, the rate of flow was increased. The patient, who was an excellent observer, said that he could feel his bladder getting fuller, almost drop by drop, but only on the right.

The subjective symptoms related to micturition referred to above ceased after the operation.

Case 24.—This patient was seen a few months after the onset of a thrombosis of the left posterior inferior cerebellar artery. As he is still alive, no histological evidence about the extent of the lesion has been obtained. Although there may be minor differences in the region of the medulla involved by thrombosis of this artery, all cases show involvement of the spino-thalamic tract. In this patient pain and thermal sensation throughout the right side of the body below the third division of the fifth cranial nerve were absent. In reply to questioning, the patient stated that he had noticed no change in any way in micturition, and that he had the usual sensation underlying the desire to micturate. However, when cystometrography was carried out, he was asked to pay attention to his sensations. He then found that he felt the sensation underlying the desire to micturate only and entirely on the left; it was located mainly in the left side of the penis. From that time onwards he realized that he experienced this sensation only on the left side, and he found that when he passed urine he felt it passing only on the left. When cystoscopy was performed later, he felt the instrument being passed only on the left. The posterior urethra was then stretched by elevation of the bridge on the instrument: on the right this caused no sensation; on the left, it caused a feeling of pricking in the left of the penis. Catheters were then pushed into the ureteric orifices, and the orifices and lower ends of the ureters were stretched; something was felt on the left, nothing on the right. A ureteric catheter was pushed into the wall of the bladder on the right side, so as to deform the whole viscus; this caused some sensation, located to the right. It should be pointed out, however, that by this time, there was some recovery of pain conduction, so that severe stimulation of the skin on the right with a pin caused a slight sensation of pain.

From Table I, it will be seen that many of those patients who had lost the normal sensation underlying the desire to micturate experienced other sensations related to bladder filling and emptying. These sensations may now be considered, under the following headings: (*a*) abnormal sensations related to bladder fullness; (*b*) sensations at a distance; (*c*) urethral sensations and the sensation underlying the desire to micturate.

Comments on Clinical Evidence

(*a*) *Abnormal Sensations Related to Bladder Fullness.*—Repeated observations were made by the patients who had lost the normal sensation underlying the desire to micturate on a certain new sensation in the lower abdomen—which might be called a substitute sensation—by means of which they were made aware of the state of tension in their bladders. It consisted of a vague feeling of fullness, poorly localized, usually described as occurring " down below ", or " in the stomach " (" stomach " being used by many people in this country as a euphemism for belly or abdomen). Further comment on this sensation will be made in the discussion; it suffices to state here that it was never confused with the normal sensation by any patient.

(*b*) *Sensations at a Distance.*—Sensations at a distance are those sensations, such as frontal headache, the feeling one is about to shiver, or that one cannot take a deep breath, which have been observed and investigated by Guttmann and Whitteridge (1947) in cases of complete division of the cord. As has been shown, such sensations occurred also in these cases, where the cord was never divided, and where only the afferent pathway from the bladder was divided.

(*c*) *Urethral Sensations and Sensation Underlying Desire to Micturate.*—It is known that in the normal subject the sensation of having a full bladder that needs emptying is related to a rise in tension of the bladder wall. But in some normal subjects various forms of stimulation of the urethra cause a desire to micturate. Such people experience this desire when a catheter or cystoscope is passed along the urethra, and particularly when its tip stretches or deforms the membranous and prostatic parts. In such circumstances, however, there is no rise in bladder tension. Yet these subjects may find that this sensation is the same as that which

they experience when their bladders are full and under tension, or they may find that it consists of only the urethral component of this sensation.

In this investigation, the sensation underlying the desire to micturate has been separated as far as possible from sensations arising in the urethra. In those patients who had bilateral lesions of the antero-lateral columns, a comparison has been made between the sensations experienced on catheterization and the sensations experienced as automatic micturition was about to start. (All these patients had lost voluntary control of micturition ; this aspect of the subject will be considered in a subsequent paper.) These sensations are listed in Table II.

It will be seen from this Table that those patients who had no urethral sensation or none but touch and stretch (the feeling of the catheter being passed or of it passing the sphincter, but without pain) had no sensation informing them of the imminence of micturition, or giving them the desire to micturate. The subject of Case 13 had the same sensation on being catheterized as she had before micturition. And the subject of Case 19 also had the same sensation on these occasions, although there were other additional sensations as the basis of a desire to micturate. It is to be noted that, with the exception of the subject of Case 16, where the sensation was probably the substitute sensation, these sensations subserving the desire to micturate all came on immediately before micturition occurred ; whereas the normal sensation subserving the desire to micturate comes on many minutes before the subject chooses to micturate. It is suggested that all these patients had in fact lost the normal sensation causing the desire to micturate, but, retaining much urethral sensation, some patients interpreted the sensations associated with changes in the urethral sphincter and/or stimulation of the posterior urethra as being the normal sensation of needing to micturate.

Histological Evidence

The cases of which the clinical accounts have been given above may be divided into groups, in order that common microscopical anatomical features can be extracted.

To determine the position of the pathways, plans of each case were drawn, showing the degenerated areas at various levels of the cord. These plans from the different cases were then superimposed, and the smallest common area of degeneration at each level was determined. All the 21 cases, of which necropsy material was obtained, were used to determine the afferent pathways. As many cases show similar areas of degeneration, only

TABLE II

SENSATIONS EXPERIENCED BY PATIENTS WITH BILATERAL LESIONS OF ANTERO-LATERAL COLUMNS ON BEING CATHETERIZED AND AT THE BEGINNING OF AUTOMATIC MICTURITION

Case No.	Sensation on Catheterization	Sensation Occurring Immediately before Micturition
1	Catheter felt ; painless	None
2	Catheter felt ; painless	None
3	Irritation and throbbing	Irritation and throbbing in urethra and vagina
4	Catheter felt ; painless	None
5	Catheter felt ; painless	None
6	Unknown	None
7	Nothing felt	None
8	Catheter felt ; painless	None
9	Catheter felt ; painless	None
10	Catheter felt ; painless	Tingling and itching in penis
11	Catheter felt ; painless	None
12	Nothing felt	None
13	Slight desire to micturate	Slight desire to micturate
14	Catheter felt ; painless	Feeling that she is about to micturate, or that she is passing urine, or the normal desire to micturate
15	Nothing felt	None
16	Nothing felt	Slight tingling in region of b.adder
17	Catheter felt ; painless	Feeling that she is about to micturate
19	Tickle in penis ; pricking at meatus; desire to micturate	Tickle in penis ; pricking at meatus ; desire to micturate ; pricking above pubis ; feeling that he is micturating ; feeling that he is stopping himself micturating

cases which are of particular value in delimiting the tracts are shown in the photographs on Plates I to IV.

In most cases the operation was performed at the fourth, fifth, or sixth thoracic segments. The position and the extent of the incision were purposely varied. It is for this reason that the extent and area of destruction of the cord at the level of the incisions differ greatly from side to side and from case to case.

The degenerated area in the region of the operation is far more extensive than at higher levels; for the incisions made into the cord may destroy not only long ascending fibres, but also descending and intersegmental fibres. Retrograde degeneration in these descending tracts usually does not extend cranially for more than about a centimetre; and so a true picture of degenerating ascending fibres is obtained cranial to this level.

Photographs of sections from representative cases are shown in Plates I to III. As far as possible the sections have been taken at comparable levels; in most cases they are from a mid-thoracic segment (usually the site of operation) and from lower and upper cervical segments. The considerable variation in the size of the cords seen in the photographs had been observed also at necropsy.

Figs. 4, 12, 13, and 14 are of sections stained by the Weigert Pal method (degenerating fibres unstained). Fig. 8c is a Gros' silver preparation showing absence of degenerated axis cylinders. All other figures are of sections stained by the Marchi method; degenerating fibres stained black.

Group 1 (a).—This group consists of cases in which the pathways conducting the sensation of a full bladder and pain from the bladder are bilaterally divided: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18; Case 19 will be considered in this group.

Cases 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, and 19 were examined histologically. Photographs of representative sections from six of these 15 cases examined histologically are shown in Plates I and II. In 13 of these cases there is no evidence of appreciable degeneration in the posterior columns. It is evident that the afferent pathways must lie within the area of degeneration that is common to all the sections at comparable levels. It therefore lies within the degenerated area in the lateral columns.

The limits of the common area of degeneration at the mid-thoracic level are shown most clearly in Figs. 3, 5, and 6; the anterior limit is shown on the right side of Fig. 5; the posterior limit on the right side of Fig. 3, and the left side of Fig. 6. The common area is shown in Fig. 15; it lies on the surface of the cord, opposite the lateral horn.

Fig. 16 shows the common area of degneration at the upper thoracic level, deduced from an examination of all 15 cases. This area maintains the same position in the cord, as at the mid-thoracic level.

At the low cervical level the common area of degeneration is shown most clearly in Figs. 4, 5, 6, and 7. The anterior limit may be determined from the right side of Figs. 4 and 5, and the posterior limit from the right side of Fig. 4, and the right side of Fig. 6. Fig. 7 suggests that the common degenerated area is a fairly narrow band. This common degenerated area lies on the surface of the cord approximately opposite the posterior angle of the anterior horn (Fig. 17). At the high cervical level the area of degeneration is fairly constant throughout the cases. It is in the form of a band extending from the posterior horn to the anterior lateral fissure approximately. Figs. 4 and 6 show that this band is divided into two by an area of intact fibres, lying a little posterior to the level of the lateral dorsal process of the anterior horn.

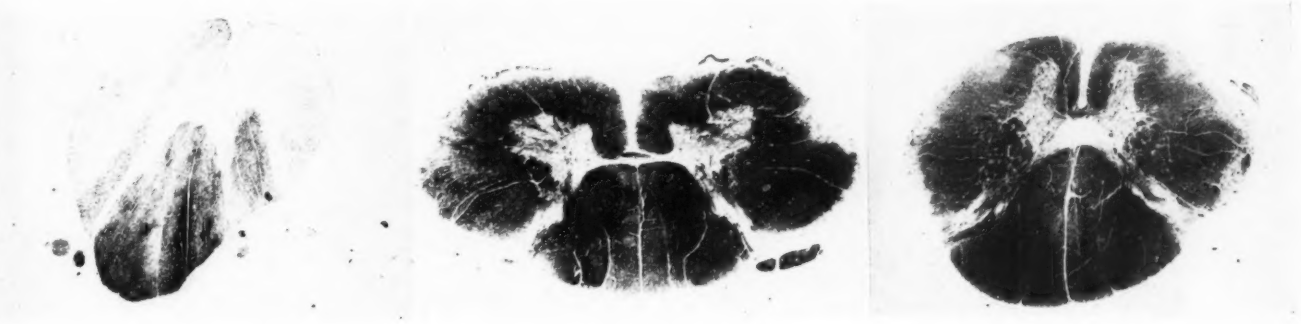
From the 15 cases so far discussed it would not be possible to determine within which part of the degenerated area the afferent pathway from the bladder runs. Cases 21, 22, and 28 allow more accurate localization to be made. In none of these cases was there any disturbance of bladder sensation. All three cases show degeneration in the most posterior zone of the lateral columns on the surface of the cord; this degeneration is particularly marked in Figs. 10 and 11. This degenerated area corresponds to the more posterior zone of degeneration described in Figs. 4 and 6. Therefore the afferent fibres under discussion cannot lie in this area, but must run in the more anterior zone of degeneration, approximately opposite the lateral dorsal process of the anterior horn (Fig. 18).

Figs. 15 to 18 show the smallest common area of degeneration at different levels of the cord in the cases with loss of the sensation underlying the desire to micturate. This area keeps in approximately the same position on the surface of the cord throughout the region studied (cervical and upper thoracic); in the thoracic region it is opposite the lateral horn, and in the cervical region opposite the lateral dorsal process of the anterior horn.

Case 19 (Fig. 8) is particularly interesting, as pain from over-distension of the bladder was felt, and, occasionally, the patient stated that he had a desire to micturate. The section of the mid-cervical region shows the area of operation on the left side of the cord. It is possible that the area of degenera-

a b c

Fig. 3. (Case 1). a: Th.4. b: C7. c: C1.



a b c

Fig. 4. (Case 5). a: Th.7. b: C7. c: C2.

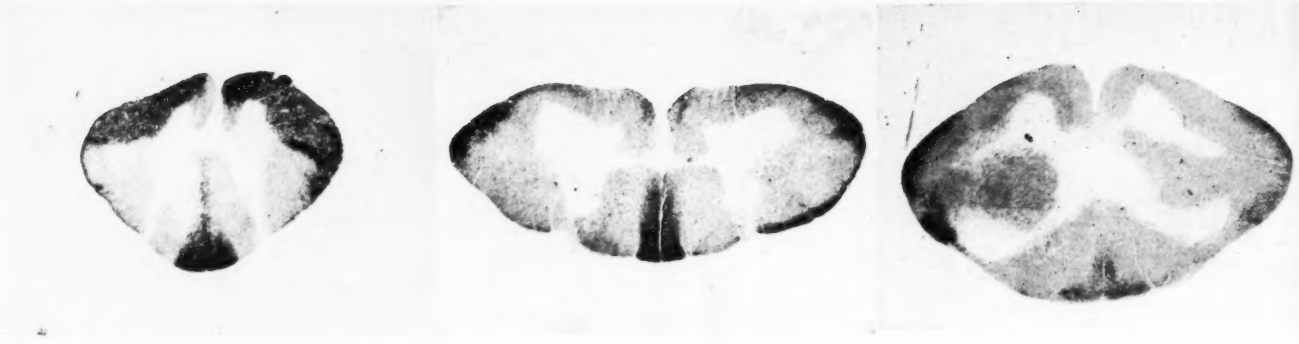
a b c

Fig. 5. (Case 6). a: Th.5 and 6. b: C7. c: C1.

All figures are photographs of transverse sections of spinal cords (× 4·25) stained to show areas of fibre degeneration. In Figs. 4, 12, 13, *and* 14 *the sections are stained by the Weigert Pal method.*

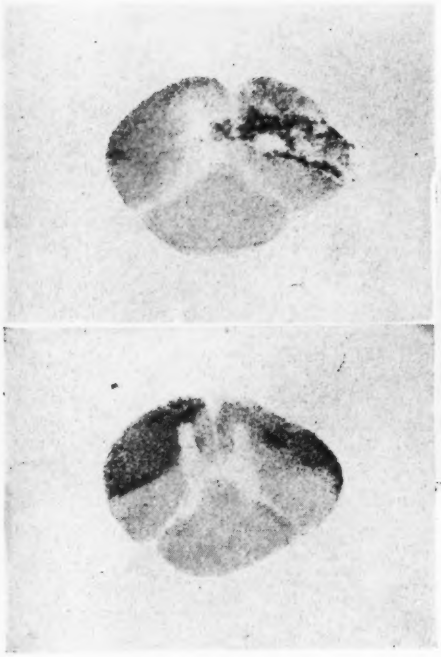
Figs. 3–8 *are from cases with bilateral lesions of the antero-lateral columns involving centripetal pathways from bladder and some centripetal pathways from urethra. In Figs.* 3–11, "*a*" *shows the region of operation.*

PLATE I

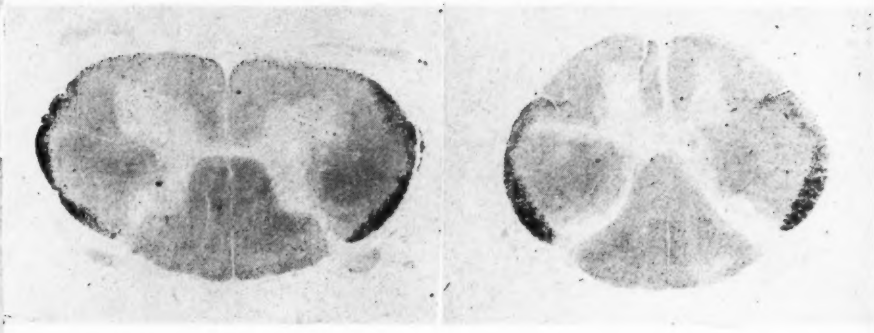


a b c

Fig. 6. (Case 10). a : Th.5. b : C7. c : C1.



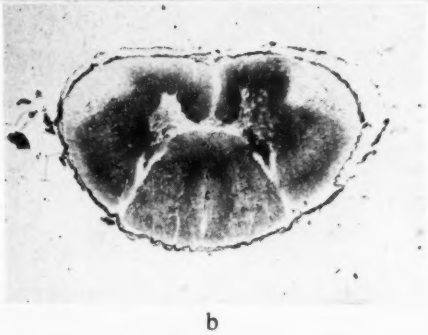
a



b c

Fig. 7. (Case 13). a : Th.9. b : C7. c : C1.

a c



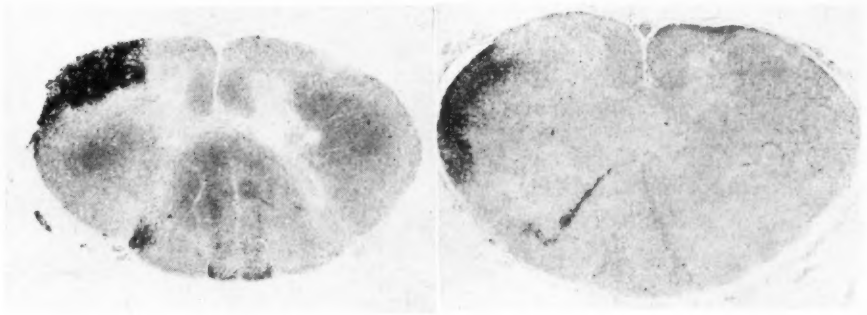
b

Fig. 8c is a Gros silver preparation. In all other Figures the sections are stained by the Marchi method.

Fig. 8. (Case 19). a : C5 and 6. b : C4. c : C1.

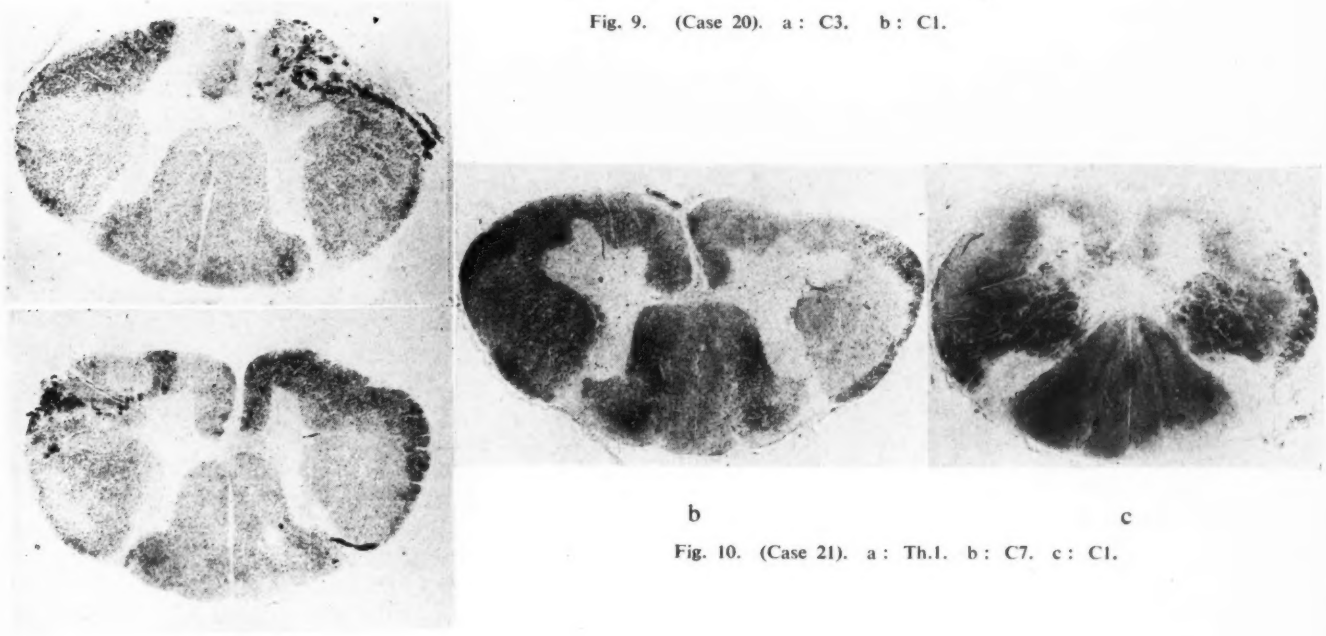
PLATE II

Figs. 9, 10, and 11 *are from cases with lesions of the antero-lateral columns, with partial or no involvement of the centripetal pathways.*



a b

Fig. 9. (Case 20). a : C3. b : C1.



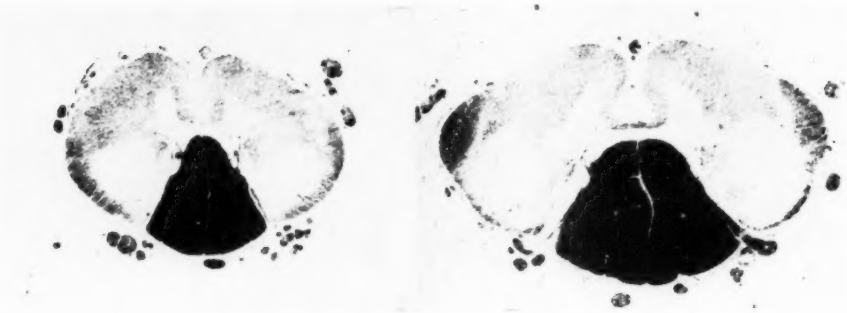
a b c

Fig. 10. (Case 21). a : Th.1. b : C7. c : C1.

a b c

Fig. 11. (Case 22). a : Th.5. b : C7. c : C1.

PLATE III



a b

Fig. 12. (Case 28). a : Th.5. b : C3.

a b c

Fig. 13. (Case 29). a : Th.2. b : C7. c : C4.

a b c

Fig. 14. (Case 30). a : Th.4. b : C7. c : C4.

Figs. 12, 13, *and* 14 *are from cases with lesions not involving the centripetal pathways.*

PLATE IV

tion on the left side does not extend as far posteriorly as the total extent of the area within which the afferent pathway lies. It is possible that a few fibres in this area were not divided. This suggestion is supported by the Gros' silver preparation of the spinal cord just rostral to the operation area. Sections prepared by this method to demonstrate axis cylinders show more precisely the limits of destruction of fibres. From these silver sections it can be seen that the area of destruction does not extend as far posteriorly as the limit of the common pathway.

Group 1(b).—This group consists of cases in which the pathways conducting the sensation of a full bladder and pain from the bladder are bilaterally intact : 28, 29, and 30. All these cases were examined histologically.

Photographs of representative sections are shown on Plate IV. This group consists of the cases that form the control. They provide further evidence of the region where these afferent fibres do not run. In Fig. 12 there is almost complete degeneration of the posterior half of the lateral columns in the high cervical level. There is no degeneration in this case in the area of the lateral columns, or on the surface of the cord opposite the lateral dorsal process of the anterior horn, where it has been shown that the afferent pathway lies. In Fig. 13 there is almost complete degeneration in the funiculi graciles, a very few anterior fibres being spared. In Fig. 14 at the high cervical level the funiculi graciles are degenerated, except for a few posterior fibres ; the mid-zone of the funiculi cuneati are also degenerated. No bladder dysfunction of any kind occurred in these cases, confirming that no afferent pathway from the bladder runs in the posterior columns.

Group 1(c).—This group consists of cases in which the pathways conducting the sensation of a full bladder and pain from the bladder are unilaterally divided : 20, 21, 22, 23, 24, 25, and 26.

Cases 20, 21, and 22 were examined histologically. Photographs of representative sections are shown on Plate III. In Case 20 (Fig. 9), the operation was unilateral ; although the degeneration includes that common area demonstrated in Group 1(a), the sensations of needing to micturate and of pain were normal. In Case 21 (Fig. 10), the area destroyed at operation is very anterior ; in Case 22 (Fig. 11) it is very posterior. In these two cases the pathway under discussion may have been sectioned on one side, but on the other side it was definitely intact. In Fig. 10 the degeneration on the left side does not involve the region under discussion ; in Fig. 11 the degenerated area on the right side might include this afferent pathway, but on the left side the pathway is definitely not involved. Thus, as far as this afferent pathway is concerned, these two cases may be treated as unilateral cases. They confirm the findings from Case 20, which shows that when the afferent pathway is divided unilaterally the subject still remains aware of the state of distension of his bladder and has the sensation of needing to micturate and the pain of over-distension.

Group 2(a).—This group consists of cases in which the pathways conducting the sensations of pain and temperature from the urethra are bilaterally divided : 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, 15, 16, and 19.

Cases 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, and 19 were examined histologically. Photographs of sections from representative cases are shown in Plates I and II. These are the same cases as have been discussed in Group 1(a), without Case 8. The smallest common area of degeneration was determined in the section dealing with Group 1(a). It is thus evident that the pathway conducting the sensations of pain and temperature from the bladder and the urethra lies within the same area of degeneration as the pathways conducting the sensation of a full bladder (Figs. 15 to 18).

Group 2(b).—This group consists of cases in which the pathways conducting the sensations of pain and temperature from the urethra are unilaterally divided : 8, 17, 20, 21, 23, and 24.

Cases 8, 20, and 21 were examined histologically. Photographs of representative sections of Cases 20 and 21 are shown in Plate III. These cases have already been considered under Group 1(c). It is seen that the pathway conducting impulses subserving pain and temperature from the urethra runs in the same region as that conducting impulses subserving the sensation of a full bladder and pain from the bladder.

Discussion

Seventeen patients with bilateral lesions of the spino-thalamic tract had lost the normal sensation underlying the desire to micturate, and the sensations of pain and temperature from the bladder and urethra. The pathway in the cord conducting the impulses giving rise to these sensations lies on the surface of the cord, approximately opposite the dorsal lateral process of the anterior horn. It lies in the same region of the cord as that conveying impulses interpreted as pain, warmth, and cold from the sacral segments of the body.

A control group of cases without lesions of the spino-thalamic tract has been given ; these cases had degeneration of spinal tracts, with normal bladder and urethral sensation. A case of subacute

combined degeneration of the cord (Case 29), and a case of Friedreich's ataxia (Case 30) show degeneration of afferent pathways with no disturbance of the sensations that concern us here. The inclusion of a case of amyotrophic lateral sclerosis (Case 28), a motor and not a sensory disorder, is justified on similar grounds: the lesions in the spinal cord serve to show where the tracts do not run. These few cases were included because clear histological specimens were available. Many other cases have been seen, with similar lesions not involving this pathway. Such patients had had no abnormality or lack of sensation from the bladder.

Thus the evidence presented shows that the centripetal tract in man lies in a region of the cord similar to where it lies in the cat. In man its position is somewhat more lateral, for it lies within the most lateral region of the cord, about midway between the anterior and posterior horns (Figs. 15 to 18). It should be possible to narrow down the region occupied by this tract still further, as more evidence is collected.

The only other evidence known to us is that of the case reported by McMichael. In his specimen the tract could not be identified in the cervical region, and was not clear in the thoracic region. In the lumbar region—the region that could not be investigated in our series of cordotomies—" Weigert Pal sections showed a bilaterally symmetrical zone of degeneration immediately anterior to the posterior cornua lying superficially in the lateral columns ". This region is similar to that in which the pathway has been located in the present investigation in the thoracic and cervical regions; but in the cases presented here, at the higher levels, it is more anterior and more lateral; for there is an area free from degeneration immediately anterior to the posterior cornua. McMichael's case is particularly im-

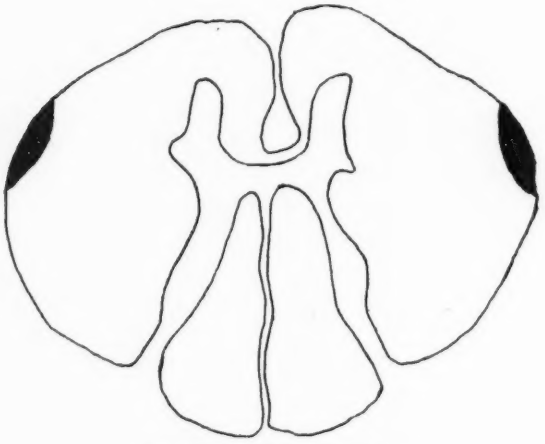


Fig. 15.—Mid-thoracic region.

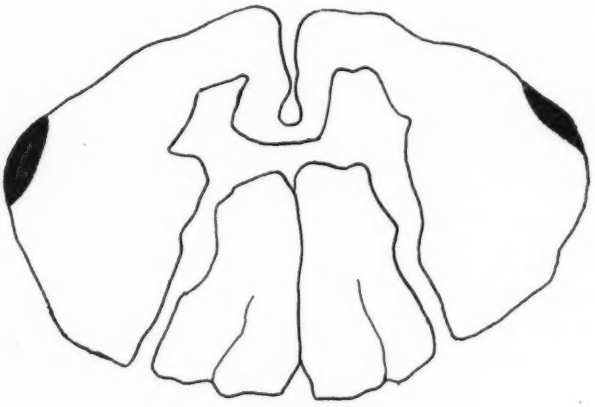


Fig. 16.—Upper thoracic region.

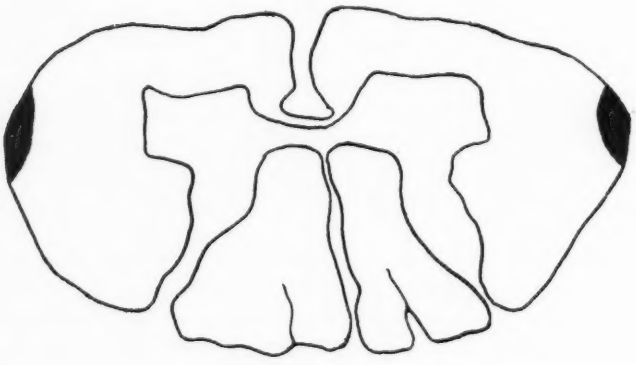


Fig. 17.—Lower cervical region.

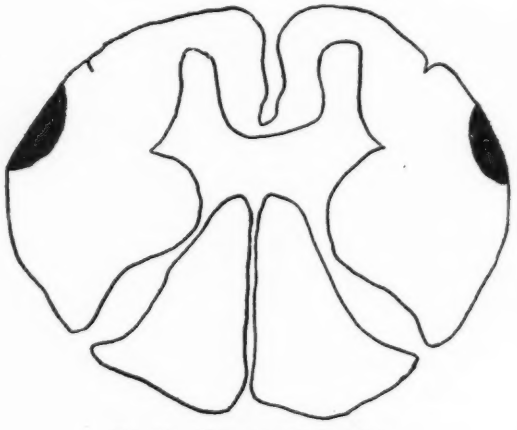


Fig. 18.—Upper cervical region.

Figs. 15–18.—Drawings of transverse sections of the spinal cord. The area containing the centripetal pathway from the bladder and the spinothalamic pathway from the urethra is shaded.

portant, as the patient had no somatic sensory loss, for it shows that the part of the lateral column conveying the centripetal path from the bladder can be divided, without there being a simultaneous division of the somatic centripetal pathway in the spino-thalamic tract.

Most patients having a unilateral lesion of the spino-thalamic tract notice no change in bladder function, and retain the normal sensation of a full bladder and desire to micturate. In all, 12 cases of unilateral cordotomy have been studied ; seven are not included in this series, as they added nothing to those described here. In five of them (Cases 20, 23, 25, 26, and 27) for some time the sensation giving rise to the desire to micturate was experienced unilaterally ; in the others no abnormality was noted. Direct questioning on the laterality of this sensation was not used, because the possibility of the sensation being unilateral had not been thought of until Case 23 was seen. Before this investigation was begun, three cases of thrombosis of the posterior inferior cerebellar artery had been studied. These patients were not questioned about the desire to micturate ; none of them spontaneously made any comments on it, or on urethral sensation. Towards the end of this investigation a further case (Case 24) was encountered. This patient in reply to questioning stated that he had the normal sensations underlying the desire to micturate, and that he felt his urine passing in the normal manner. He was then investigated in accordance with the scheme employed for the cases of this series. The patient then noticed that when he was catheterized, he felt the passage of the catheter only on the left, which was the side of the body having normal sensation. As his bladder was filled, he was then surprised to find that he experienced the desire to micturate only on the left. From the experience of this case, one is inclined to wonder whether the other cases of posterior inferior cerebellar artery thrombosis might not have had this sensation unilaterally had their attention been directed to their sensations ; during cystometrography there is ample time for observing sensations while the bladder is being slowly filled. Two of the patients with unilateral cordotomy (Cases 26 and 27) experienced this sensation unilaterally only when the desire to micturate became urgent enough to force itself on their attention.

To account for the discrepancy in the evidence of these six patients, who felt the sensation underlying the desire to micturate unilaterally, and that of other patients with a unilateral lesion feeling the sensation centrally and not unilaterally, one may consider two possibilities. It could be that a vague and poorly localized sensation, such as that underlying the desire to micturate, is felt centrally and bilaterally, whatever the anatomical pathway subserving it ; for it could be that for a sensation that has for years been central and bilateral a pattern of perception has become so fixed that it over-rides the perception of an innovation in the sensation. Or it might be that, in some cases, this pathway from one side of the bladder runs up both sides of the cord, while in others it runs up the opposite side of the cord only.

From unilateral cases, it was learnt that the pathway conducting impulses subserving the sensation of pain from the lower ends of the ureters, from the walls of the bladder, from the urethra, and thermal sensation from the urethra, also runs in the spino-thalamic tract, and in the same region as that conducting the sensation underlying the desire to micturate.

Patients in whom the pathway in the spino-thalamic tract has been divided, may retain the sensation that micturition is impending, that it is progressing, and that it has ceased. These sensations are doubtless due to impulses arising in the urethral mucosa and in the sphincter urethrae membranaceae and the large group of perineal muscles that act synergically with the sphincter. Such impulses doubtless travel via the posterior columns.

It remains to answer the question : why do not all patients, after bilateral spino-thalamic cordotomy, have urethral sensation, giving them knowledge that micturition is starting, progressing, and stopping.

Immediately after division of both spino-thalamic tracts patients may have no sensation from bladder or urethra. This occurs more commonly in women than in men, and is likely to be due to the fact that women have shorter urethras than men, with less length of mucosa. This condition may last a month or more, and patients who die in this period have therefore regained no urethral sensation. Those living past this stage tend to feel more. The removal, by division of the spino-thalamic tracts, of all sensation from the bladder, and the greater part of sensation from the urethra—for the sensations of pain and warmth and cold are the predominant urethral sensations—demands from the patients a re-orientation to the sensations perceived. Similarly in the sphere of somatic sensation, many patients lose the ability to tell sharp from blunt ; but others do not. Also, the feeling of wetness is difficult to perceive after spino-thalamic division, doubtless due to the removal of thermal sense ; but some patients learn to know when something is wet, while others do not—both having the same sensory apparatus. After cordotomy a new sensory pattern from the urethra is presented to consciousness ;

not all patients become equally adept in interpreting it. Its interpretation depends on the ability to carry out minute observations on one's own sensations. Further, the patients' ability to explain what they feel enters into the question of what sensation is regained; probably patients often experience sensations of greater complication than they are able to describe.

As has been noted in the histories of these patients, there is a vague sensation related to distension or rise in pressure in the bladder, which we have called, non-committally, a substitute sensation. We do not propose discussing this sensation further here; work is continuing on the origin of the sensation, and the pathway by which the impulses subserving it reach the cerebrum. It is sufficient to point out that wherever these impulses arise, they do not travel in the spino-thalamic tract.

It remains to discuss Case 19, the patient who lost the normal desire to micturate, and who was found, within 24 hours of the operation that cut off the sensation of pain from the rest of his body below the fourth thoracic segment, to be suffering from great pain due to distension of the bladder. Although there was good recovery of urethral sensation, urethral pain was not regained; and so the pain of distension of the bladder cannot be attributed to urethral sensation. As has been mentioned when considering the histological evidence, it is probable that a few fibres, at least on one side, lying posteriorly, escaped cutting at operation. One is unwilling to draw too definite a conclusion from one case, with regard to a possible separation of pathways subserving pain and pathways subserving the desire to micturate. As further evidence is collected, it may become possible to draw further conclusions about the detailed topography of these tracts.

Before finishing this discussion on pathways of conduction of impulses that are interpreted as sensation, it is of importance to remember that the sensation of having a full bladder that needs to be emptied, can, like all sensations, be evoked by psychic factors. This was shown clearly by one of our patients, the subject of Case 9, who, although she had no sensation from her distended bladder, experienced the sensation of needing to micturate, whenever she saw or heard the bed-pans being taken round the ward.

Summary

The location within the spinal cord of man of the following afferent pathways has been determined: (*a*) that subserving the sensation that the bladder is full, giving rise to the desire to micturate; (*b*) that subserving the sensations of pain from the bladder, urethra, and lower end of the ureter, and sensation of temperature from the urethra; (*c*) that subserving touch and pressure or tension from the urethra. The pathways considered under the headings (*a*) and (*b*) lie within the spino-thalamic tract on the surface of the cord opposite the dorsal lateral process of the anterior horn. The pathways considered under (*c*) lie within the posterior columns.

We wish to express our gratitude to Mr. Wylie McKissock for his whole-hearted cooperation; he operated on the majority of these patients, and, while relieving their pain, maintained a scientific attitude, which greatly aided the investigation, of which this paper is the first report.

We are grateful to the many surgeons and pathologists who have helped us in this work; and particularly to Mr. O'Connell, Professor Norman Dott, Mr. Dickson Wright, Mr. Norman Matheson, Mr. E. A. Turner, Mr. Malcolm Donaldson, Dr. J. G. Greenfield, Dr. W. Blackwood, Dr. W. G. C. Mair, and Professor W. D. Newcomb. We wish to thank Mr. P. B. Ryan for carrying out a number of the cystoscopies. We are also grateful to Dr. E. A. Carmichael, who helped us by providing the facilities for this investigation and by his interest and criticism. Our thanks are due to the Medical Committee of the National Hospital for Nervous Diseases for allowing us to use their case records.

We wish also to thank Mr. F. J. F. Barrington and the Editor of *Brain* for permission to reproduce Fig. 1.

To our technical assistants, Mrs. J. A. Mills and Miss Kathleen Harrison, we wish to express our gratitude for their careful and painstaking work; and we also wish to thank Mr. J. A. Mills for giving us the benefit of his experience of histological techniques and photography.

Patients 6, 11, 13, 19, 24, 25, and 27 were in the National Hospital; their case numbers were respectively 18299, 23011, 16162, 12166, 30790, 26668, and 16148.

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RETROGRADE AXONAL CHANGES OF THE DE-AFFERENTATED NUCLEUS GRACILIS FOLLOWING MID-BRAIN TRACTOTOMY

BY

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While retrograde cell changes in the central nervous system are well known, degeneration of that portion of the axon which lies central to a lesion is very seldom observed. For this reason the relevant histological observation of two human cases is recorded here.

In both cases the operation of mid-brain tractotomy had been performed by one of us (R.A.B.) on the right side, involving the medial fillet on this side. It was of great histological interest to find that Marchi degeneration had not only occurred in the medial fillet above the lesion, but that there was also retrograde degeneration towards the left nucleus gracilis. This type of Marchi degeneration, referred to in the literature as " retrograde ", is of considerable practical and theoretical interest. Opinion about its occurrence differs widely, as Combs (1951) has recently pointed out. The following two cases seem to throw light on the occurrence of this phenomenon.

Material

A description of the degenerative changes in certain fibre tracts in the material of R.W. and M.W. has already been made (for the central tegmental tract see Glees and Zander, 1950 ; for the spinothalamic tract see Glees and Bailey, 1951).

Case 1.—R. W. was suffering from a malignant metastasis of the second lumbar vertebra, which led to painful paraplegia. To relieve the pain, a mid-brain tractotomy on the right side was perform ed on August 17, 1949, and a lateral chordotomy on the left side at the level of the fourth thoracic segment on August 24, 1949. The patient died on October 4, 40 days after the last operation and 49 days after tractotomy.

Case 2.—M. W., aged 28, became ill in 1948 with pain in both legs and backache. Exploratory laminectomy was carried out in July, 1949, and adhesions of the spinal cord and of the cauda equina, caused by a malignant disease, were found. Right mid-brain tractotomy was performed on October 26, 1949. Death occurred on June 27, 1950, eight months after this operation.

Methods

The brain and spinal cord in both cases were subdivided into various small blocks, some of which were used for Marchi impregnation (Swank and Davenport, 1935), while others were stained with the Weigert method. The Nissl method (cresyl violet) and a silver impregnation (Glees, 1946) were also used.

Histological Findings

In R.W. a malignant growth involving the second lumbar vertebra had caused compression of the cauda equina, while in M.W. the infiltration of the roots and meninges of the cauda equina by a tumour had compressed the spinal cord itself. Marchi degeneration had occurred in the posterior columns, as well as degeneration of other tracts (Fig. 1). In both cases a mid-brain tractotomy had been carried out on the right side (Fig. 2), causing a subsequent ascending degeneration of the medial fillet ; we were however surprised to find that Marchi degeneration extended also into the pons and medulla towards the left nucleus of Goll (Fig. 3). The degeneration just below the level of the mid-brain lesion was at first scanty, but increased at medullary level and was very conspicuous close to the nucleus gracilis, while no such degeneration could be traced towards the nucleus cuneatus.

With regard to its topographical position, the retrograde degeneration was found to occupy in each case a ventral and lateral position in the interolivary space and, at pontine level, a more lateral and somewhat ventral position in relation to the undegenerated fibres of the medial fillet (Fig. 4).

Striking changes can also be seen in the Nissl picture (Fig. 5). When one compares the nuclei graciles of both sides and the nucleus gracilis on the left with the left nucleus cuneatus, one sees that the medial side of the left nucleus gracilis is for the greater part denuded of cells and that those cells which are present show various chromatolytic changes and are shrunken, with dark, diffusely

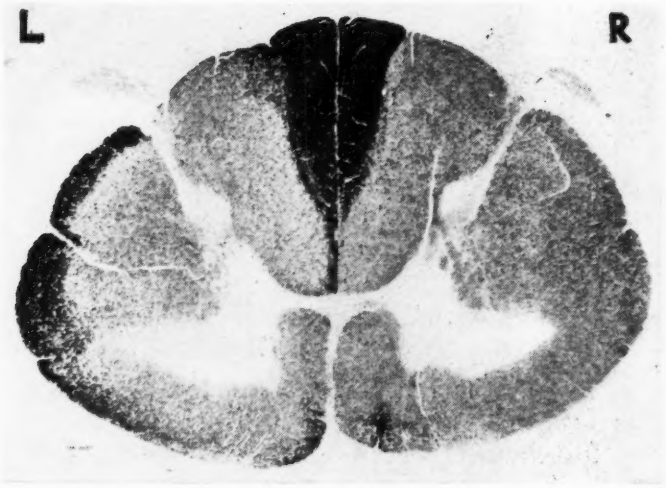

FIG. 1.—The Marchi degeneration at the fifth cervical segment of R. W. Both fasciculi graciles are heavily degenerated. The degeneration on the left dorso-lateral and ventro-lateral part of the cord is due to a chordotomy at the level of the second thoracic segment.

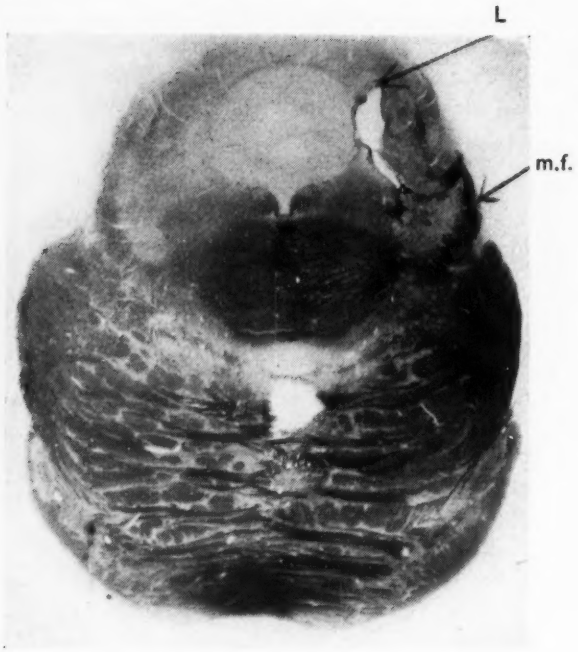

FIG. 2.—Level of the mid-brain tractotomy in R. W. Compare with Fig. 6f.
(L = lesion caused by operation ; m.f. = medial fillet)

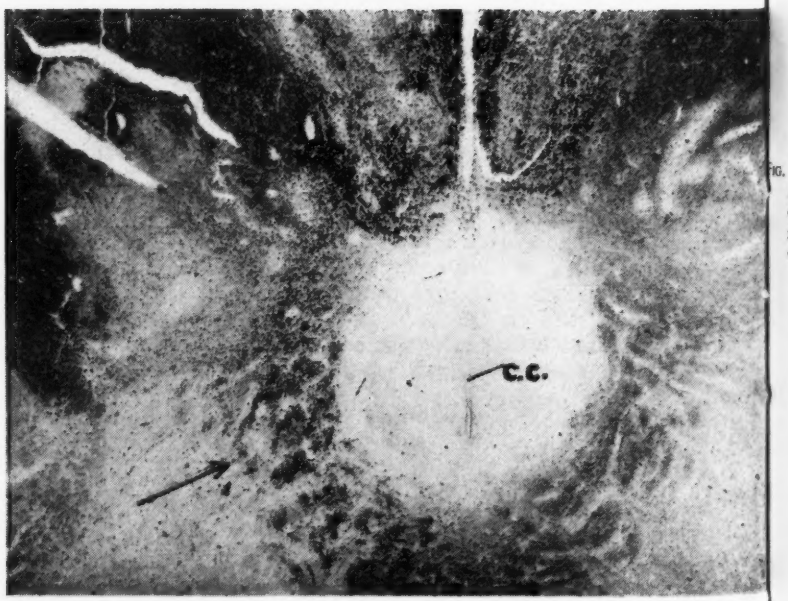

FIG. 3.—The retrograde Marchi degeneration in the case R. W. Both graciles nuclei show an equal amount of Marchi degeneration, but retrograde axonal changes are seen only on the left side and are marked with an arrow.
(c.c. = central canal)

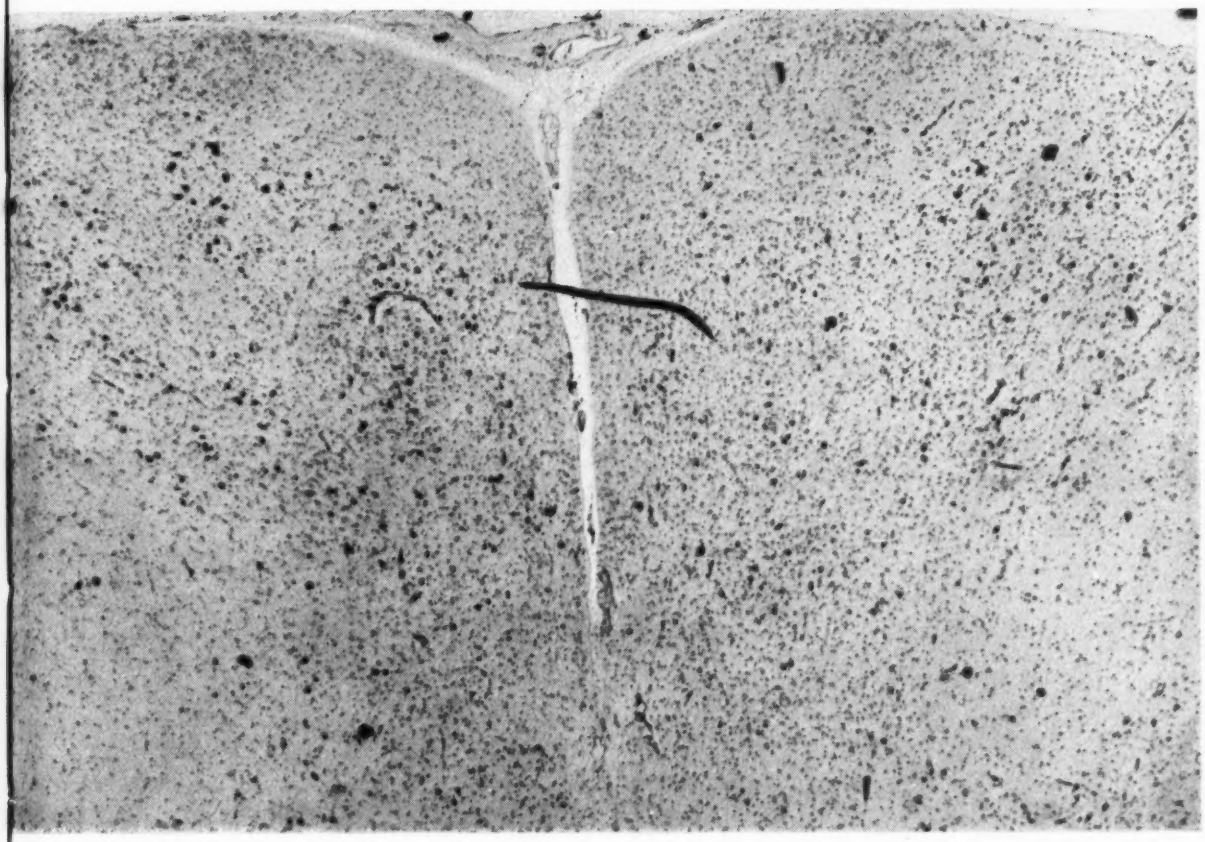

FIG. 5.—A Nissl picture of the lower portion of the medulla of M. W. under low power. The left nucleus gracilis is on the right side of the picture. Many of its cells are gone and those present show marked degeneration under higher power.

FIG. 4.—Medulla, Marchi of Case 2 (M. W.). Arrow 1 marks the position of the retrograde degeneration originating from the left nucleus gracilis, and arrow 2 the degenerated tegmento-olivary tract following mid-brain tractotomy.

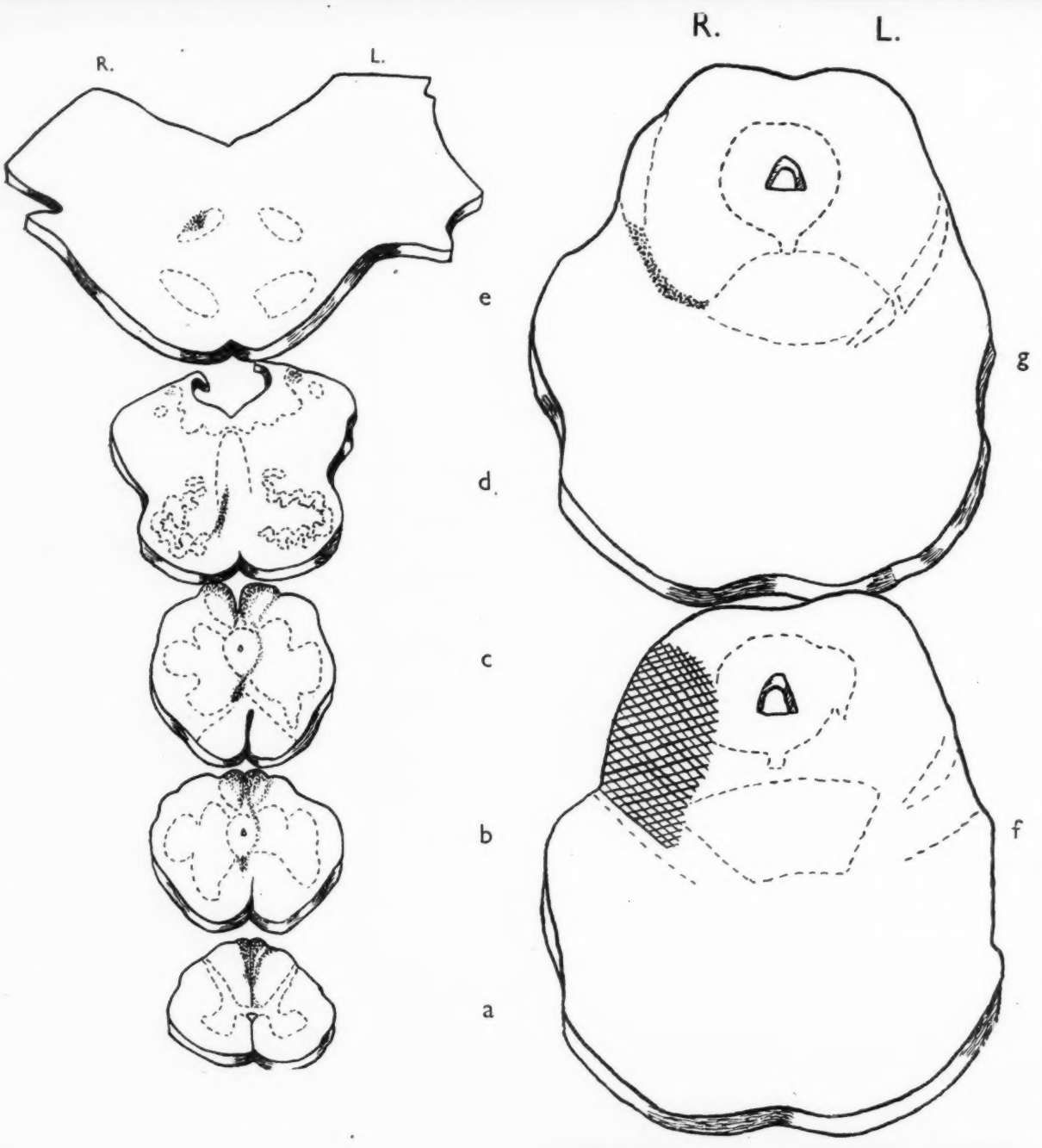

FIG. 6.—Diagram drawn from slides, using the microprojector, of Case 1 (as seen from above).

a = degeneration in the posterior columns; b = their terminations in the nucleus gracilis; b, c, d, e = retrograde degeneration; f = the tractotomy lesion at mid-brain level; g = the degeneration in the medial fillet resulting from the tractotomy lesion.

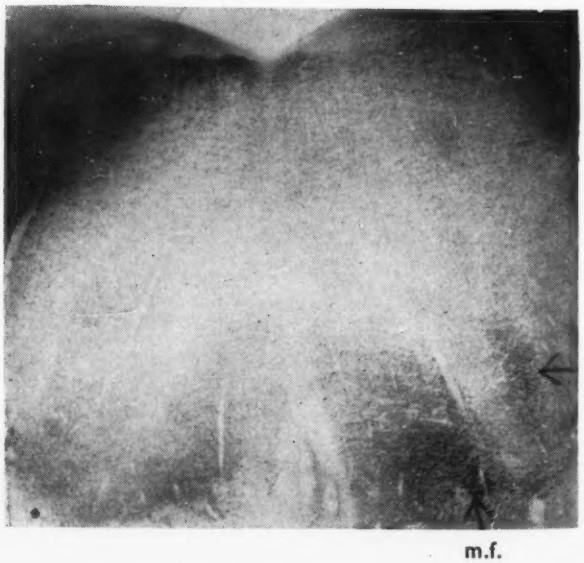

FIG. 7.—The retrograde degeneration of a portion of the right medial fillet in Case 2 (M. W.) at lower pontine level. Compare with Fig. 6e. Note that the amount of retrograde degeneration is less than at medullary level.
(tr. t.o. = tractus tegmento-olivaris; m.f. = medial fillet)

staining cytoplasm and small nuclei. The cell changes in the left nucleus gracilis are more severe than in the left nucleus cuneatus, where chromatolytic changes can also be seen. In the silver picture, swollen axons—some of them fragmented—can be seen emerging from the left nucleus gracilis. The silver picture corresponds to that of the Marchi preparations in that it shows the retrograde axonal changes, although the Marchi picture is more obvious.

Discussion

The fact that retrograde degeneration occurred after de-afferentation and partial cutting of the axon is of great theoretical interest. In some ways the present cases illustrating this retrograde Marchi degeneration assume the condition of an ideal experiment. Axonal amputation by cutting the right medial fillet at mid-brain level has affected the neurons of both nucleus gracilis and nucleus cuneatus on the left side. Chromatolytic changes in response to axonal severance can be seen in both nuclei. However, retrograde Marchi degeneration of the remaining portion of the axon originating from cells of the cuneate nucleus did not occur, while it could be clearly observed in fibres whose parent cells had both de-afferentation, due to degeneration of the fasciculus gracilis, and a cutting of the axon at mid-brain level. Furthermore, the right fasciculus gracilis was also degenerated to the same extent as the left, but as no axonal damage had involved cells of the right nucleus gracilis no degeneration (of a retrograde type) of the myelin sheath could be detected.

We would like to stress that the ascending Marchi degeneration of the fasciculi graciles was of the same density on both sides in each case and produced an equal amount of de-afferentation, as we assume that the posterior column nuclei have their afferents in posterior column fibres only (Glees, Livingston, and Soler, 1951 ; Glees and Soler, 1951).

Observations on the lateral geniculate body by Le Gros Clark (1932), Minkowski (1913) and others have shown that transneuronal cell changes follow de-afferentation. This has recently been clearly stated by Penman and Smith (1950) in their work on the trigeminal nuclei. The right nucleus gracilis also shows changes which must be attributed to transneuronal degeneration ; but in spite of these cell changes retrograde Marchi degeneration does not appear.

The conclusions are therefore obvious. To obtain retrograde Marchi degeneration axonal cutting is apparently not enough, but only if the main afferent impulses to the parent cells are also cut does this degeneration occur.

The problem of retrograde changes in the central portion of the fibre have been discussed by Spatz (1920, 1921), who found that after cutting ventral roots the retrograde changes were not limited to the anterior horn cells, but also became apparent in the fragment of the axon central to the cut. Spielmeyer (1922) supports the observations made by Spatz. Brodal (1939), when studying the retrograde cell changes in the inferior olive after cerebellar lesions, saw no retrograde axonal signs and says that there is no unanimous view concerning the retrograde changes in that part of the axon still connected with the cell. Brodal quotes Raimann (1900) and Pilcz (1899), who believe that the changes are only very slow, and he too quotes the findings of Spatz.

Taking our material into account we would like to suggest that cutting the axon combined with de-afferentation may prove to be an excellent means of finding out whether one nucleus is served by one incoming source only, as seems to be the case with the nucleus gracilis. This has been pointed out in a paper to appear shortly (Glees and Soler, 1951), in which the synapses of the nucleus gracilis are investigated. We found that the terminating fibres in this nucleus originated from the fasciculus gracilis only.

Much of the experimental work done by one of us (P.G.) has been carried out with the Marchi technique. In none of that material could retrograde Marchi degeneration be seen. This might be due to the fact that the survival time after operation was comparatively short. However, even in experiments where we allowed a considerable survival time in order to see how long a Marchi positive stain could be obtained (Glees, 1943), no retrograde degeneration was to be seen.

We have already pointed out that axonal cutting was not enough to produce retrograde Marchi degeneration, but that de-afferentation seems also to be required. It should however be stressed that even if these two conditions are fulfilled a considerable time elapses before retrograde degeneration becomes apparent. This fact is borne out by the present cases. The survival time after tractotomy in the case of R.W. was 49 days and eight months in M.W. The retrograde fibre changes are more marked in M.W. Furthermore, in both cases they are more conspicuous towards the parent cells of the fibres involved. We assume that de-afferentation and axonal cutting will eventually cause cell death with retrograde Marchi degeneration of the central axonal stump, but that this process takes a considerable time, and we also gained the impression that the proximal segments are involved first. Should this be the case, the mode

of this type of retrograde degeneration may be slightly different from that found in fibres of the pyramidal system (Glees, 1948), where the Wallerian degeneration, appearing already at the third day, affected every part of the fibre almost simultaneously from the lesion to the periphery, while the retrograde degeneration seems to progress distally from the cell body.

As was to be expected, the fibres showing retrograde Marchi degeneration originating from the left nucleus gracilis occupied a definite position in the brain stem. This finding is of help in localizing the position of the fibres of the nucleus gracilis in relation to those of the nucleus cuneatus (Figs. 5, 6). The fibres from the nucleus gracilis lie ventral and lateral to fibres of the nucleus cuneatus and occupy a similar position to that which Ferraro and Barrera (1936) pointed out for the monkey and Glees, Liddell, and Phillips (1951) found in the cat.

Summary

Two patients with a chronic lesion of the lower spinal cord had subsequently a right mid-brain tractotomy and survived for 49 days (R.W.) and eight months (M.W.) respectively. Retrograde fibre changes of that part of the medial fillet which originates from the left nucleus gracilis were seen, as well as death of the parent cells in the nucleus gracilis.

No retrograde changes were apparent in Marchi preparations in fillet fibres originating either in the left nucleus cuneatus or in the right nucleus gracilis or cuneatus.

While chromatolytic changes in the parent cells after axonal cutting will invariably occur, our material indicates that cell death combined with retrograde fibre changes of the central portion of the axon is certain only if there has been both de-afferentation and axonal cutting.

Our thanks are due to Miss A. G. Smith, Mr. T. A. Marsland, Mr. A. Austin, and Miss C. C. Boulter for their help.

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THE LOCALIZATION OF SOME ACID PHOSPHATASES IN BRAIN TISSUE

BY

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The histological study of phosphatase distribution began when Gomori (1939) and Takamatsu (1939) independently published a technique for the demonstration of alkaline phosphatase in tissue sections. This method was extended to the localization of acid phosphatase under normal and pathological conditions (Gomori, 1941). Wolf, Kabat, and Newman (1943) studied the distribution of this enzyme with special reference to the nervous system, and Bodian and Mellors (1944) found changes in phosphatase activity in chromatolytic nerve cells. Critical studies by Danielli (1946) have confirmed the validity of the general technique, but Stafford and Atkinson (1948) showed that there was a considerable loss of phosphatase activity during acetone or alcohol fixation. Doyle (1948) found that acid phosphatase was distinctly better preserved by dehydration in the frozen state than after such fixation. A procedure for freezing tissue at liquid air temperatures and dehydrating in a vacuum suggested by Altmann was developed by Gersh (1932) and subsequently modified by several investigators. Studies on the distribution of acid phosphatase in chemically fixed material have given diverse results and it would seem, therefore, that tissue prepared by a freeze-drying procedure and submitted to a modification of the Gomori technique, taking into account the criticisms by Martin and Jacoby (1949) and Danielli (1950), would yield more reliable results. In the application of such a method it is necessary to adapt the Altmann-Gersh technique to preserve, as far as practicably possible, the histological integrity of brain tissue. In addition, the significance of the final result depends upon the provision of optimal conditions for the activity of the enzymes under investigation.

The non-specific phosphatase demonstrable by glycerophosphate has formed the subject of much earlier work in chemically fixed tissue. Other more specific phosphatases have been observed by biochemical methods. Those acting on adenosine esters are of particular importance in view of the participation of these compounds in a number of metabolic processes. A 5-nucleotidase has been described in extracts of brain (Reis, 1934), and adenosine monophosphate (5-adenylic acid) was used in this study to demonstrate it. The importance of adenosinetriphosphatase has been established, and Meyerhof (1948) has attributed a controlling role to it in glycolysis. This enzyme was found to be bound to particulate elements of brain homogenates (Meyerhof and Wilson, 1948). The present paper describes and illustrates results obtained from localizing in brain tissue the sites of enzymatic phosphate liberation from glycerophosphate at *p*H 5·3, from adenosine monophosphate at *p*H 6·5, and from adenosine triphosphate at *p*H 6·5.

Method

The freeze-drying technique used consisted in rapid freezing of thin slices of tissue followed by removal of the ice by sublimation under high vacuum.

Normal, young, adult male and virgin female white rats were used. The animals were anaesthetized with ether, and the calvarium was removed. The brain was then enucleated; 2 mm. thick coronal sections were cut with new safety razor blades and frozen in isopentane (Simpson, 1941) at −35°C. within 20 seconds.

After not more than 10 minutes the blocks were removed with appropriately shaped lengths of platinum wire which were themselves first cooled. The pieces of brain were then quickly laid on a bed of degassed paraffin wax (m.p. 49°C.) in a specially designed glass tube which attaches to a phosphorus pentoxide trap mounted on an Edwards 2S.50 high vacuum pump. The tube was then surrounded by a vacuum flask containing phenyl ethyl ether (phenetole) brought down to a temperature of −78°C. by means of solid carbon dioxide. The pump was started, and drying continued for three days. After about six hours the phenetole bath had risen to a temperature of −30°C. at which it was maintained by the periodic addition of solid carbon dioxide. At the

* Holder of research grant from the Medical Research Council under the Mapother Bequest.

end of 72 hours the vaccum flask was removed and the material was left for about two hours to warm up toward room temperature. The tube was then isolated from the pump by closing a valve. The wax was melted cautiously by means of a water bath and embedding continued for 15 minutes under water pump pressure.

Paraffin blocks were made in the usual way. All the paraffin material was stored at −10°C. in a dessicator. Sections, 7–15μ thick, were cut on the same day on which they were required for the chemical procedures from blocks stored for less than a week. The blocks were cooled before being cut on the microtome as the resulting rigid sections could be more easily mounted onto albumenized slides without the use of water.

Dewaxing was carried out immediately before incubation in petroleum ether (boiling range 80–100°C.) for two minutes followed by two rinses in isopentane (boiling range 27–31°C.). The sections dried immediately on contact with air and became paper-white within two to five seconds. They were then thrust into the incubation media (previously warmed to 37°C.) with a sharp movement to avoid the adhesion of air bubbles.

The general procedure was to incubate these specially prepared sections in media containing a single phosphoric acid ester, from which the active enzyme split phosphate. Lead ions were added to the incubation medium so that this phosphate was precipitated at the site of liberation as lead phosphate. This precipitate was then converted to a visible product.

The substrate media were prepared directly before use. They each contained a phosphoric acid ester, a lead salt required to precipitate the liberated phosphate and a buffer.

The composition of the media is given in Table I and they are compared in Table II.

Coplin staining jars containing the slides in 30 to 60 ml. of medium were placed in an incubator set to 37°C. Sections were removed at various intervals for treatment whereby the precipitated phosphate was converted to lead sulphide which is brown.

The slides were washed for 10 minutes in four changes of iced distilled water, placed in cold dilute yellow ammonium sulphide solution (1 ml. in 50 ml. of water) for two minutes, and rinsed again in iced distilled water. The sections were rapidly dehydrated through the alcohols, followed by 15% cyclohexanol in petroleum ether, and by petroleum ether (boiling range 80°–100°C.) alone. They were mounted in " clearax " (Gurr) dissolved in petroleum ether.

Glass-distilled water was used throughout. The adenosine triphosphate (Boots) used in this work was stored as the barium salt (Ba_2 ATP $4H_2O$) at −78°C. When required it was reprecipitated to remove the decomposition products and converted to the sodium salt by the use of an ion exchange resin (Bailey, 1950). Zeokarb 216 resin (2·5 g.) in a 15 ml. column was converted to the acid form with 5N-HCl and washed with glass-distilled water until the *p*H of the effluent was greater than 5·0. All subsequent operations were carried out at 0°C. The barium salt of adenosine triphosphate (200 mg.) was dissolved in 2N-HCl (5 ml.) and diluted with water (10 ml.). The solution was brought to *p*H 6·5 with N-NaOH and centrifuged. The washed precipitate was redissolved in 3 ml. of 2N-HCl and 5 ml. of water. This solution was passed through the resin column and washed through with water (25 ml.). The effluent was neutralized with N-NaOH, diluted to 50 ml., and stored at −78°C. After analysis the solution was diluted so that it contained 124 μg. labile phosphorus per millilitre. Commercial samples of adenosine monophosphate (B.D.H.) were sufficiently pure and were used as 0·005 M aqueous solution neutralized with NaOH and stored at −78°C. Glycerophosphate containing a mixture of approximately equal parts of the α and β isomers was of sufficient purity. The stability of the stock solutions was checked by frequent *p*H determinations.

Incubation periods at 37°C. covered a wide range of times. Sections were removed at intervals, usually forming a logarithmic series : 10, 20, 40, and 80 minutes. These times were found to be suitable for adenosine

TABLE I

COMPOSITION OF THREE MEDIA EMPLOYED

Glycerophosphate pH 5·3	
0·1 M sodium acetate buffer (*p*H 5·3) ..	15 ml.
0·04 M lead acetate (neutral)	1·5 ml.
0·1 M stock solution glycerophosphate ..	1·5 ml.
0·1 M magnesium chloride	1 ml.
water .. .. to	30 ml.
Adenosine triphosphate pH 6·5	
0·002 M stock solution adenosine triphosphate	7·5 ml.
0·1 M sodium succinate buffer (*p*H 6·5) ..	15 ml.
0·04 M lead acetate (neutral)	0·75 ml.
water .. to ..	30 ml.
Adenosine monophosphate pH 6·5	
0·005 M stock solution adenosine monosphate	3·0 ml.
0·1 M sodium succinate buffer (*p*H 6·5) ..	15 ml.
0·04 M lead acetate (neutral)	1·5 ml.
water .. to	30 ml.

TABLE II*

COMPARISON OF THREE MEDIA EMPLOYED

Phosphate Ester	Glycero-phosphate	Adenosine Triphosphate	Adenosine Mono-phosphate
*p*H	5·3	6·5	6·5
Ester ..	0·005	0·0005	0·0005
Pb. ++ ..	0·002	0·001	0·002
Mg. ++ ..	0·003	—	—
Buffers :			
Acetate ..	0·05	—	—
Succinate	—	0·05	0·05

* All figures in molar concentration.

triphosphate and glycerophosphate but for adenosine monophosphate a range of 10 to 40 minutes was adequate.

After preliminary work on a large number of animals these conditions were used to obtain the results to be described.

Rapid freezing ensures accurate localization by reducing possible enzyme diffusion and conserves maximum activity. The anaesthetized brain is less liable to stimulation during sectioning and freezing. An initial freezing temperature of −65°C. for 2 mm. sections was least liable to cause tissue damage and was consistent with good histology. Adequate tissue preparations also depend upon the duration of vacuum drying which appears not to be critical, but three days under the conditions described gave satisfactory results.

The time and temperature of embedding were not varied. The paraffin blocks retained their activity in storage without appreciable loss, whereas microtome sections deteriorated rapidly. Water and the aqueous alcohol solutions used in the usual dewaxing processes were found to have a detrimental effect on the experimental material. This difficulty was overcome by the use of a low boiling point wax solvent.

The medium containing glycerophosphate was substantially the same as that described by Gomori (1941, 1946). The other media were found experimentally to provide optimal conditions for qualitatively different staining in the minimum time. Inconsistent results were obtained when the adenosine triphosphate used in the incubation medium had not been reprecipitated. Variation of the *p*H level of the substrate media within the acid range did not alter the characteristics of the localizations but retarded the reaction. The short incubation times made possible by preserving enzyme activity and the employment of optimal conditions reduced the possibility of diffusion. Those elements of tissue left unstained by each of the three procedures at short incubation times took on stain at prolonged incubation periods so that differences in localization at first striking became progressively reduced.

Control of the tissue activity in the various media was obtained by omission of the phosphoric acid ester, by washing or heating the tissue, by chemical pretreatment with trichloracetic acid, and especially by the use of enzyme inhibitors acting at relatively low concentrations. Sodium fluoride (10^{-3} M) was used in control media with glycerophosphate and uranyl acetate (10^{-3} M) in the adenosine triphosphate and adenosine monophosphate control media. If the ester were omitted from the substrate medium the staining was amorphous and negligible in quantity. Complete suppression of staining could be produced by adding to the substrate medium the inhibitors in the concentrations stated.

Results

The following findings, which are sites of lead sulphide deposition, were observed consistently in 20 consecutive animals when the experimental conditions were accurately followed. Tissue from each animal was incubated with all the experimental and control media.

Glycerophosphate Substrate.—Sections incubated in this medium showed staining mainly in the neuronal cytoplasm (Fig. 1A).

The cerebral cortex showed the characteristic cortical cytoarchitecture extremely well. The cells were clearly defined and stood out sharply against an unstained background. Some dendritic processes stained for short distances from their cell bodies. The cytoplasm stained intensely, but the nucleus remained unstained although well demarcated. The nucleolus and some karyosomes were as darkly stained as the cytoplasm. In the pyriform lobe staining of nerve cells appeared deeper than elsewhere in the cortex. In the corpus striatum and diencephalon there was a pale staining of the background which was more pronounced in the thalamus and hypothalamus than in the striate body and globus pallidus. The nuclei within the thalamus and hypothalamus varied in their degree of staining, although individual cells differed in no discernible respect from cortical neurons. The supraoptic nucleus of the hypothalamus (Fig. 8), the nuclei paraventralis reuniens, and the medio-dorsalis of the thalamus were all darker than other diencephalic nuclei.

Throughout the midbrain, pons, and medulla neurons of the cranial nerve nuclei stained deeply and showed those details demonstrated by the cortical neurons (Fig. 2A).

In the cerebellum Purkinje cells and the basket fibres were almost selectively stained (Figs. 3A and 4). The nucleolus of the Purkinje cells stained most deeply, the nucleus next, and the cytoplasm least. The basket fibres were as deeply stained as the nucleoli of the Purkinje cells. The granules showed little staining and at the time when the basket fibres were deep brown they appeared as light brown discrete cells.

Glial cells were evident throughout the whole brain, but stained only moderately. At none of the incubation periods employed did they approach the depth of staining reached by neuronal cytoplasm or cerebellar basket fibres.

Nowhere in the brain were the walls of the parenchymal vessels seen at short incubation times, but at such times as would make the Purkinje cells dark brown the nuclei of vessels walls appeared. The nuclei of meningeal vessel walls appeared darker than those of the smaller parenchymal vessels. All elements of the choroid plexus showed deep staining. The nuclei of ependymal cells lining the ventricles, unlike neuronal nuclei, showed greater staining than the cytoplasm of these cells.

Apart from the basket fibres and the proximal parts of the dendrites of larger neurons no other fibres could be made out when tissue was incubated

for less than three hours: prolonged incubation led to fibre staining.

Adenosine Triphosphate Substrate.—All nuclei, wherever situated in the brain, appeared to show staining in some degree. Just as in material incubated with glycerophosphate the cytoplasm stood out in clear contrast to an unstained background, tissue incubated with adenosine triphosphate for short incubation times showed clearly demonstrable nuclei alone (Fig. 1B).

Most deeply stained were muscle nuclei in vascular walls, nuclei of ependymal cells, neuronal nucleoli and the astrocytes. At short incubation periods nuclei of vascular walls, neuronal nucleoli, and astroglia appeared to be the only elements demonstrable. Longer incubation periods of between 40 and 60 minutes produced staining of the neuronal nuclei but these nuclei remained lighter than glial nuclei. Neuronal nucleoli, however, were as dark as the glial elements (Fig. 2B). Interfascicular oligodendroglia had the same depth of staining as the neuronal nuclei.

When tissue was incubated with glycerophosphate some diencephalic nuclei stained more deeply than others, but with this substrate there was no variation in their degree of staining. In the cranial nerve nuclei the cytoplasm of individual cells showed slight staining but more than the cytoplasm of cortical or diencephalic neurons.

In the cerebellum the glial elements of the molecular layer were intensely stained and consequently very deep brown, and those glial cells in close association with the Purkinje cells were darker than the remaining cells (Figs. 3B and 5). At longer incubation times the Purkinje cell cytoplasm was only a moderate brown, but the nuclei were darker than the cytoplasm and the nucleoli darkest of all. There was usually an aggregation of darkly staining discrete particles at the perikaryon. The granular cells stained moderately and scattered through them were discrete deeply staining particles. The medullary centres of the folia were unstained but the glial cells between the fibres were a pale brown.

The choroid plexus was deeply stained in all its elements. Ependymal nuclei showed deep staining and nerve fibres none.

Adenosine Monophosphate Substrate.—Sections incubated in this medium showed staining mainly in the nerve fibres (Fig. 1C).

The corpus callosum and the fimbrial fibres of the hippocampus were the deepest staining structures and the fibres radiating from the corpus callosum were conspicuous. The larger nerve fibres appeared to stain more deeply than the finer ones, and those tracts considered to be most heavily myelinated appeared darkest.

The nerve cell bodies remained almost completely unstained (Fig. 2C). Only after incubation periods as long as 40 minutes did the neuronal nucleoli, but not cytoplasm, and glial nuclei appear.

In the cerebellum the Purkinje cells were left completely unstained except for the nucleolus (Fig. 3C), and were surrounded by intensely staining basket fibres. The molecular layer appeared as dark as the medullary centre, but neither of these elements approached the depth of staining to be seen in the hippocampal fimbria.

Ponto-cerebellar fibres and fibres of the spinal root of the trigeminal nerve were among the lightest of the fibre tracts (Fig. 6). Fibres of the cranial nerves in their intracerebral course were also very light. In the hippocampus the bands of fibres within the hilus of the Ammon's horn stained in varying degrees (Fig. 7).

At long incubation periods exceeding 60 minutes glial cells became visible, and at periods beyond that became as dark as callosal fibres. Cytoplasm of neurons was not seen even at these lengthy incubation periods.

The choroid plexus stained deeply in all its elements. The vascular walls stained only faintly at optimal incubation times.

Discussion

Three distinct localizations have been described depending upon which phosphoric acid ester was used in the incubation medium. That these findings represented the result of enzyme action was confirmed by the absence of staining on omission of the substrate ester and by its suppression with low concentrations of inhibitors. Marked differences in the sites of staining in the three cases precluded the possibility of phosphate formed by enzyme action being precipitated as lead phosphate at foci of crystallization in nuclei and other such formed elements. Thus, additional controls were available.

Previous work on this subject has been concerned largely with the localization of non-specific acid phosphatase. The varied results given by work carried out in the acid range on tissue fixed in formalin, acetone, or alcohol makes their assessment difficult, particularly in view of the considerable but uncertain destructive effect of these fixatives on the enzymes. A comparison of the results presented in this communication with those so far obtained by usual biochemical and centrifugation techniques is not strictly possible. Further, the microscopical appearances of frozen dried tissue

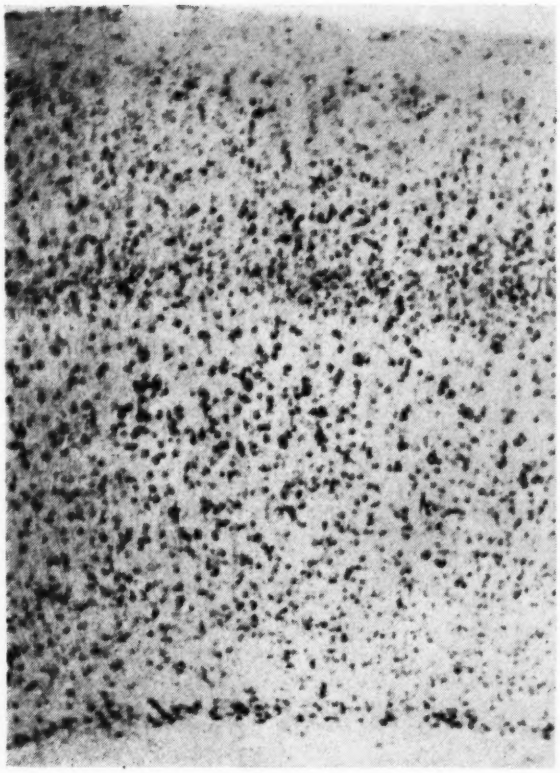


FIG. 1*a*

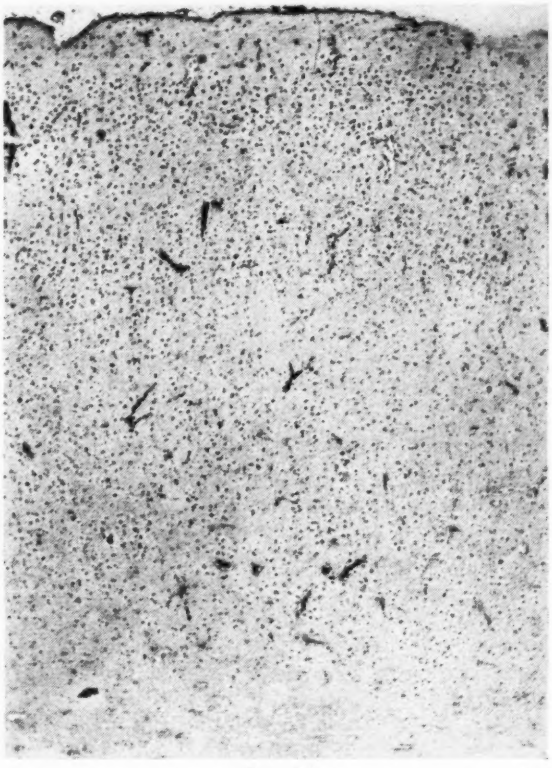


FIG. 1*b*

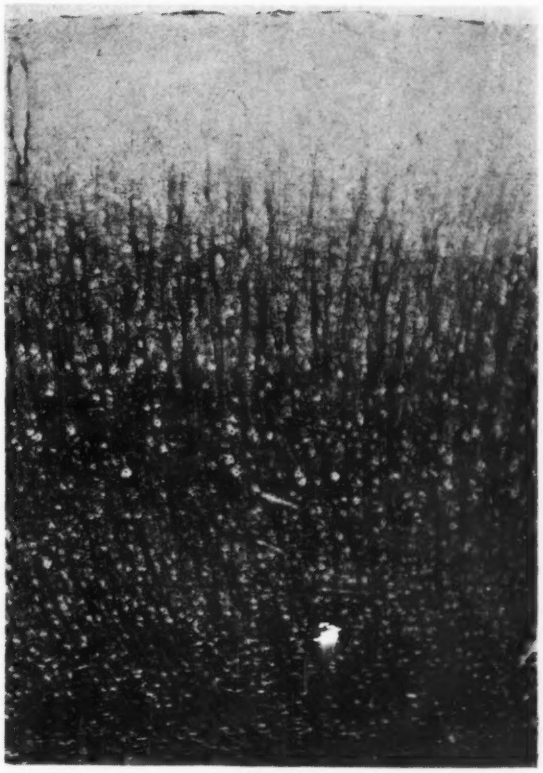


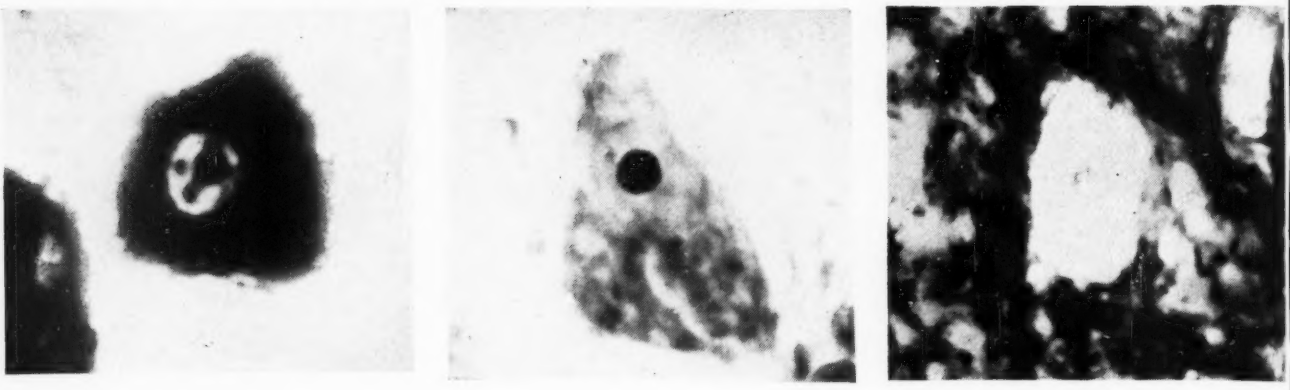
FIG. 1*c*

Fig. 1 : *Cerebral Cortex* ×50

a. Glycerophosphate substrate, showing deep staining of the neuronal cytoplasm and moderate glial staining.

b. Adenosine triphosphate substrate, showing staining of glial, neuronal, and vascular wall nuclei.

c. Adenosine monophosphate substrate showing staining of nerve fibres. Nerve cell bodies, except for their nucleoli, are left unstained.



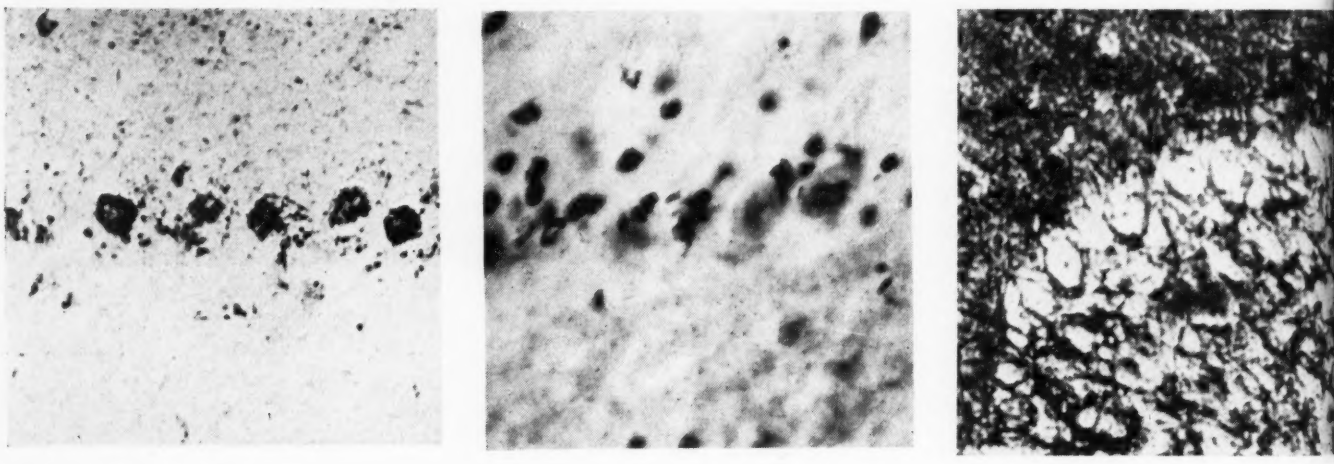
a *b* *c*

Fig. 2 : *Single Neuron from Hypoglossal Nucleus* ×500

a. Glycerophosphate substrate, showing staining of the cytoplasm, nucleolus, and some karyosomes.

b. Adenosine triphosphate substrate, showing staining of the nucleolus and light staining of the cytoplasm.

c. Adenosine monophosphate substrate, showing, except for a faint nucleolus, an unstained nerve cell body.



a *b* *c*

Fig. 3 : *Cerebellar Cortex* ×150

a. Glycerophosphate substrate, showing staining of the Purkinje cells and basket fibres.

b. Adenosine triphosphate substrate, showing deep staining of the Bergmann glial and nucleoli of Purkinje cells.

c. Adenosine monophosphate substrate, showing staining of nerve fibres and nucleoli of Purkinje cells.

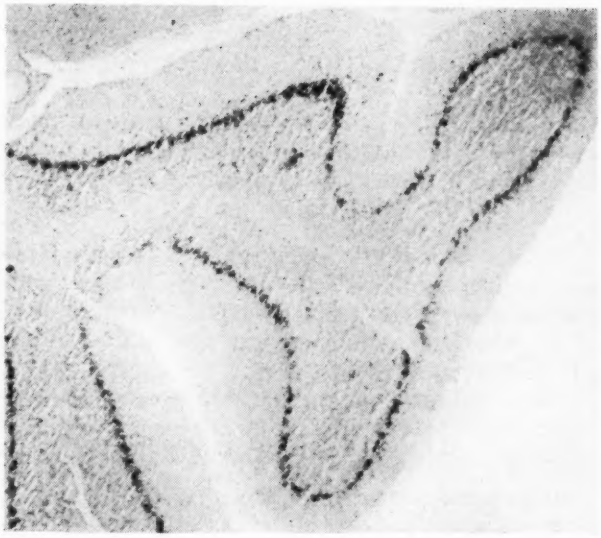


Fig. 4 : *Cerebellar Cortex* ×45

Glycerophosphate substrate, showing almost selective staining of the Purkinje cells.

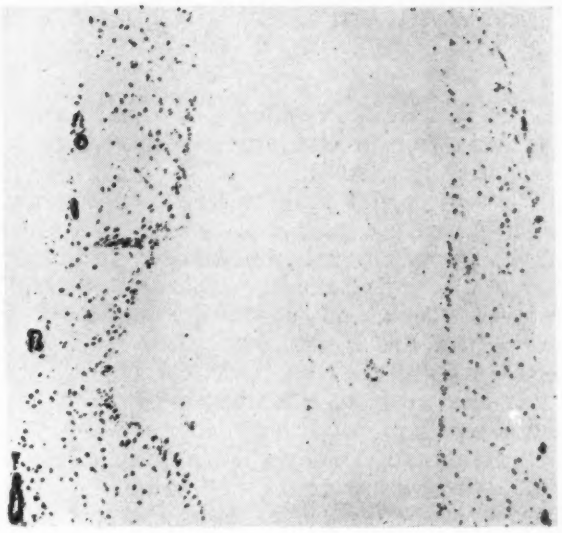
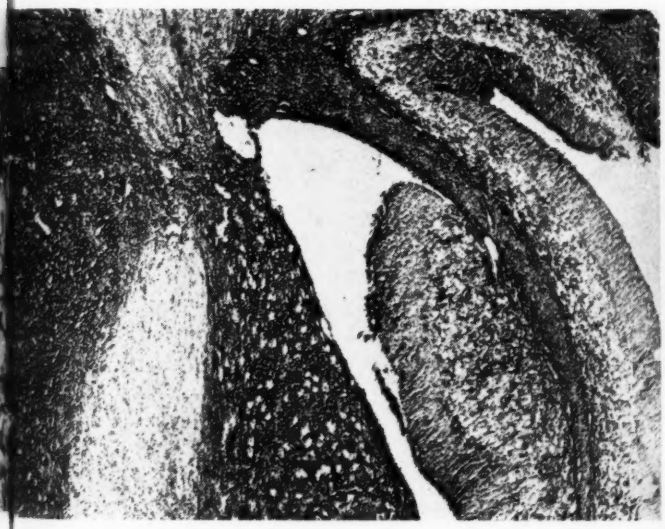


Fig. 5 : *Cerebellar Cortex* ×70

Adenosine triphosphate substrate, showing faintly staining glial cells in the medullary centre, an unstained granular layer, and deeply staining glial and vascular wall nuclei in the molecular layer.



. 6 : *Ponto-Cerebellar Angle* ×45

Adenosine monophosphate substrate, showing light staining of ponto-cerebellar fibres and the descending root of the trigeminal nerve. The medullary centre and molecular layer of the cerebellar cortex stain, whereas the granules and the nerve cell bodies of the ventral cochlear nucleus do not.

Fig. 7 : *Hippocampus* ×40

Adenosine monophosphate substrate, showing bands of fibres staining in varying degrees.

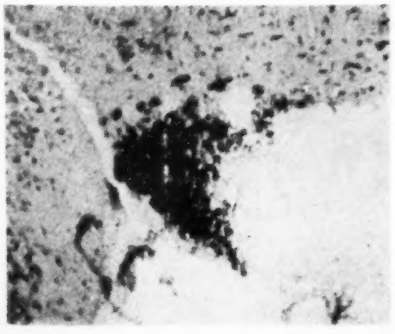


Fig. 8 : *Supraoptic Nucleus* ×50

Glycerophosphate substrate showing deep staining of the supraoptic nucleus.

do not entirely correspond with those found in the usual formalin-fixed material, a difference which warrants further study.

Various physiological processes are associated with the acid phosphatase activity of cells and, in general, protein formation is related to such activity. The metabolism of cellular nucleic acids necessarily involves the action of several enzymes: an example of this is provided by the study of the development of the Nissl substance. Chromatolysis after axon section is accompanied by a great increase in non-specific acid phosphatase and this increase is also demonstrable during regeneration. Although earlier work on the localization of non-specific acid phosphatases gave divergent results the findings described in this paper substantiate some of the previous conclusions.

The idea that the oligodendrocyte is in some way concerned with the maintenance of the myelin sheath is widely accepted. It has been postulated similarly for a considerable time and recently re-stated by Folch (1947) that the astrocytes, particularly the protoplasmic type, function in an analogous way to the nurse cells found among insecta: that is, cells whose function it is to maintain other cells. In view of this hypothesis it is of interest that astroglial cells show high enzyme activity when incubated with adenosine triphosphate. This energy-rich ester is important in the metabolism of the brain, and yields some 12,000 calories per mol on hydrolysis.

Comment on the presence of an enzyme-splitting adenosine monophosphate in the nerve fibres is not possible until more is known about the physiological significance of this compound.

The study of the nervous system by the use of these new techniques is still in the early stages of development and established findings are relatively few. Such methods, however, seem to us to hold promise for the future.

Summary

The histological distribution of acid phosphatase activity has been studied in rapidly frozen and vacuum-dehydrated brain tissue. The main site of enzymatic phosphate liberation from glycerophosphate was in the cytoplasm of neurons. Glial and neuronal nuclei were the main site of adenosine triphosphate cleavage, and adenosine monophosphate was split mainly in nerve fibres.

We are grateful to Professor Alfred Meyer and Dr. H. McIlwain for their interest in and encouragement of this work. Technical assistance was ably rendered by Miss Joyce Hinton.

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EFFERENT CONNEXIONS OF THE HUMAN PREFRONTAL REGION WITH REFERENCE TO FRONTO-HYPOTHALAMIC PATHWAYS

BY

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This paper was initiated by the necropsy of a case in which an ablation (topectomy) of the frontal pole, more or less confined to area 10/FE, had been carried out by one of us (J. Le B.). Such cases with circumscribed lesions give an almost unique opportunity of studying the connexions of certain areas with lower centres which, in the human brain at least, are by no means well established. Previous reports on the afferent thalamic connexions of area 10/FE have been conflicting (Walker, 1940a and b ; Freeman and Watts, 1947 ; Meyer, Beck, and McLardy, 1947 ; McLardy, 1950). Its efferent systems have recently been investigated by one of us (Beck, 1950) with particular reference to the prefronto-pontine system. The present case gives a welcome opportunity of checking previous results and clarifying controversial points. It will be seen that it also throws some new light on fronto-hypothalamic connexions which have received special attention lately (Le Gros Clark and Meyer, 1950) and which are of particular interest to the psychiatrist searching for the rationale of neuro-surgical operations in mental patients.

For comparison of the anatomical data one case of rostral leucotomy, as practised by Mr. McKissock in this country, has been included. This operation aims at undercutting areas 9/FDm and 10/FE, although, as will be seen later, a slightly wider region has been isolated in this particular case. The brain was specially suitable for comparison, since the age of the patient and the survival period were almost identical.

In cases with short survival the best method for studying secondary degeneration is silver impregnation. In this investigation as well as in previous ones from this laboratory, Glees' ammoniacal silver method (Glees, 1946) has proved of great value. The difficulties encountered in the evaluation of silver preparations have been sufficiently stressed by a number of authors including Le Gros Clark and Meyer (1947), Meyer (1949), and Nauta (1950). The material presented in this paper impregnated well. Negative findings in a given area could safely be regarded as proof of the absence of any fibre connexion with the ablated or isolated region ; on the other hand only an accumulation of grossly degenerated fibres and/or terminals was taken to signify the existence of such a connexion.

The primary lesions were evaluated microscopically ; the Brodmann numerals* inserted in the diagrams Figs. 2 and 4, correspond to the actual cytoarchitectonic structure as observed in the sections. Since in both cases the lesions were fairly symmetrically placed in the two hemispheres only one side has been studied ; the left hemisphere in Case 1, the right hemisphere in Case 2.

Observations on Case Material

Case 1.—M.O. was a woman, aged 67, who died 11 days after bilateral ablation of area 10/FE for intractable pain following trigeminal herpes zoster. The patient suddenly collapsed half an hour after a small routine blood transfusion and died.

Macroscopic Description.—The general appearance of the brain was normal (weight 1,270 g.) ; the arteries of the base showed no atheroma. Removal of the cerebellum and bisection of the cerebral hemispheres, however, revealed a circumscribed softening in the posterior parts of the right gyri hippocampus and fusiformis, and in those portions of the lingual gyrus and the cuneus which include striate and parastriate cortex. Histological investigation showed that there were also circumscribed lesions in the lateral thalamic nucleus and lateral geniculate body.

Ablation of the frontal poles had been carried out almost symmetrically to a depth of approximately 2·5 cm. on the left and 2 cm. on the right side (Fig. 1).

* These cases were demonstrated at the meeting of the Physiological Society held on December 16, 1950, at the Middlesex Hospital, London.

* The terminology used in the text is that of Brodmann and Economo, and Koskinas and, for the orbital surface, that suggested by one of us (Beck, 1949). From the diagrams Economo and Koskinas' symbols have been omitted.

FIG. 1.—Macroscopic appearance of the ablated frontal poles in Case 1.

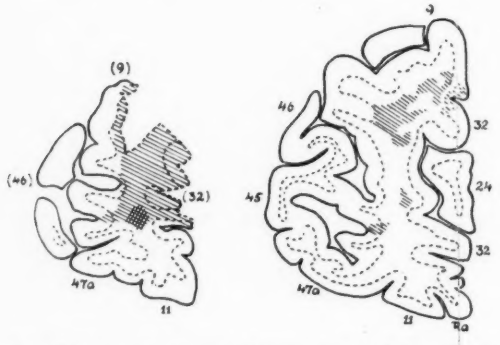

FIG. 2.*—Diagram of the posterior extremity of the left lesion in coronal sections (Case 1). The gaping sulci on the left of each drawing were filled by subarachnoid haemorrhage.

Apart from complete destruction of area 10/FE the lesion encroached upon anterior portions of area 9/FDm dorsally and areas 32/FDL and 24/LA medially. The orbital surface, areas 47 anterior, 11 and recta anterior, was not involved. A coronal cut at the level of the posterior extremity of the lesion (Fig. 2) revealed a small subarachnoid haemorrhage in the depth of the left inferior frontal sulcus, the right hemisphere being intact at this level. There was no evidence of any further damage at this or more posterior levels of the frontal lobes, and apart from the softening in the right temporo-occipital region, the rest of the brain appeared normal.

Microscopic Description: Left Hemisphere.—The full length of the hypothalamus was investigated at nine representative coronal levels. There was no significant evidence of fibre or terminal degeneration in any of its nuclei.

The thalamus was investigated at seven representative levels, from the most anterior extremity of the anterior nucleus to the level of the posterior end of the dorso-medial nucleus. A small focus of terminal degeneration was found in the anterior portion of the dorso-medial nucleus adjacent to the pars magnocellularis (Fig. 3). Within this focus degeneration was severe (Fig. 6). No further degeneration was seen in the rest of the dorso-medial nucleus or in any of the other thalamic nuclei.

The prefronto-pontine tract as defined by Beck (1950) was studied at three representative coronal levels; namely in the ventral portion of the posterior limb of the internal capsule adjacent to the nucleus ventralis lateralis, at its descent into the cerebral peduncle, and at its termination in the small medial fascicles of the pons. It appeared perfectly normal at each level (Figs. 9 and 11). In the pons many normal terminals could be seen.

The frontal cortex, immediately posterior to the lesion, showed terminal degeneration in its whole circumference, most marked laterally. Degenerated pericellular plexuses were seen in all layers, being slightly more numerous in the deeper layers. Degenerated terminals most frequently appeared as solid, bulb-like structures and only isolated rings could be seen. Many of the radial bundles showed a number of grossly degenerated fibres. In blocks taken 1 cm. and 2·5 cm. still further posteriorly, from areas 8/FC and 6/FB respectively, degeneration was no longer apparent. Degenerated fibres were seen crossing in the genu corporis callosi.

Slight degeneration occurred in the medial portion

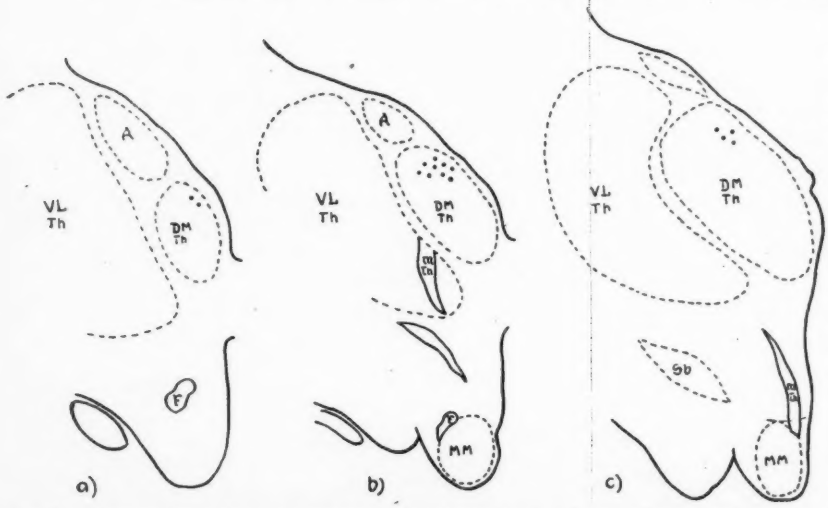

FIG. 3.—Diagram indicating the secondary degeneration in the dorso-medial nucleus of the left thalamus of Case 1 (dotted area).

The following abbreviations are used in the text figures:

A = nucleus anterior thalami; Arc = nucleus periventricularis arcuatus; DM = nucleus dorso-medialis hypothalami; DM Th = nucleus dorso-medialis thalami; F = fornix; FL = fasciculus lenticularis; FTh = fasciculus thalamicus; IC = capsula interna; LH = nucleus lateralis hypothalami; MM = nucleus mamillaris medialis; MTh = tractus mamillo-thalamicus; O Tr = tractus opticus; P = pedunculus cerebrale; PA = nucleus paraventricularis; PH = area posterior hypothalami; Ra = area recta anterior; Sb = corpus subthalamicum; SO = nucleus supraopticus; Tb = nucelus tuberis; VL Th = nucleus ventralis lateralis thalami; VM = nucleus ventralis medialis hypothalami; Z = zona incerta; III = ventriculus tertius.

** In this and Fig. 4 the extent of the surgical lesion has been indicated by cross and single hatching according to its severity.*

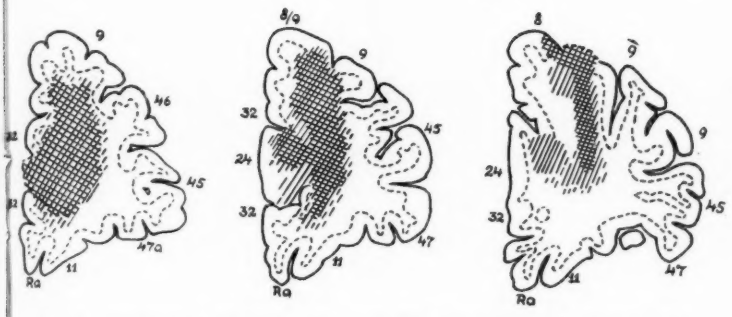

FIG. 4.—Diagram of the surgical lesion in the right prefrontal area in Case 2.

of the superior longitudinal fasciculus and in the fasciculus cinguli. The latter, however, was probably directly involved in the lesion at its pregenual portion. The uncinate and subcallosal fasciculi showed no significant degeneration.

Other regions investigated included the subthalamic nucleus, zona incerta, Forel's fields H1 and H2, and the substantia nigra, all of which were normal.

The lesion in the right temporo-occipital region presented the appearance of a fairly recent ischaemic necrosis (probably less than one week old), with degenerated nerve cells, occasionally showing ischaemic change, marked endothelial and early astrocytic proliferation. It was strictly confined to an area supplied by the posterior cerebral artery although, despite a search, no thrombosis could be found in this artery or any of its branches. It may, however, have been missed. In this position the lesion could not have contributed to any of the secondary degeneration in the left hemisphere described above.

All arteries of this brain, particularly those of medium and small calibre, showed distinct adventitial fibrosis. There was no appreciable excess of lipofuscin in the nerve cells nor were senile plaques or Alzheimer's neurofibril change found.

Case 2.—E.L. was a woman, aged 68, who died from asphyxia, following inhalation of vomitus, 10 days after bilateral rostral leucotomy for involutional depression.

Macroscopic Description.—The general appearance of the brain was normal (weight 1,390 g.). There was no obvious atrophy and no atheroma of the arteries of the base.

The leucotome entry marks were visible in the dorsal aspect of area 9/FDm, the left one lying about 4 mm. from the midline, the right one about 15 mm. On coronal section the lesion (Fig. 4) in the right hemisphere was seen to terminate at the level of the pregenual gyrus cinguli. Here it occupied the dorso-medial segment of the hemisphere sparing the orbital region at this level. One half centimetre further anteriorly, however, the lesion extended into the medial orbital region, thus occupying the entire medial half of the hemisphere, but completely sparing the lateral half. It terminated within the frontal pole in a similar medial position. Fibres from areas recta anterior, 11, 32/FDL, 24/LA, 10/FE, 9/FDm, and most anterior 8/FC were involved, while those from areas 47 anterior, 46/FDΔ and 45/FDτ were probably spared.

Microscopic Description: Right Hemisphere.—The whole length of the hypothalamus was investigated at seven representative coronal levels (Fig. 5). In contrast to Case 1 considerable fibre and terminal degeneration was observed in the ventro-medial and lateral hypothalamic nuclei. Furthermore there was a slight degeneration in the dorso-medial hypothalamic nucleus and in the medial mammillary nucleus (Figs. 7 and 8). Degenerated fibres could be traced forward in the region of the medial forebrain bundle and diagonal band to the level of the anterior commissure. A few degenerating fibres were present in the putamino-caudate junction below the internal capsule. There was no degeneration in the anterior hypothalamic area nor in the periventricular arcuate nucleus. The remaining hypothalamic nuclei also appeared normal.

The thalamus was investigated at five representative levels from the anterior tip of the anterior nucleus to the level of the centre median nucleus. In comparison with Case 1 there was more widespread though less severe fibre and terminal degeneration in the anterior half of the dorso-medial nucleus. The nuclei ventralis anterior and lateralis were normal, as were the fine-fibred fascicles traversing them on their way to the dorso-medial nucleus (Meyer, 1949). No degeneration was seen in several levels of the anterior thalamic nucleus.

The prefronto-pontine tract was found to be severely

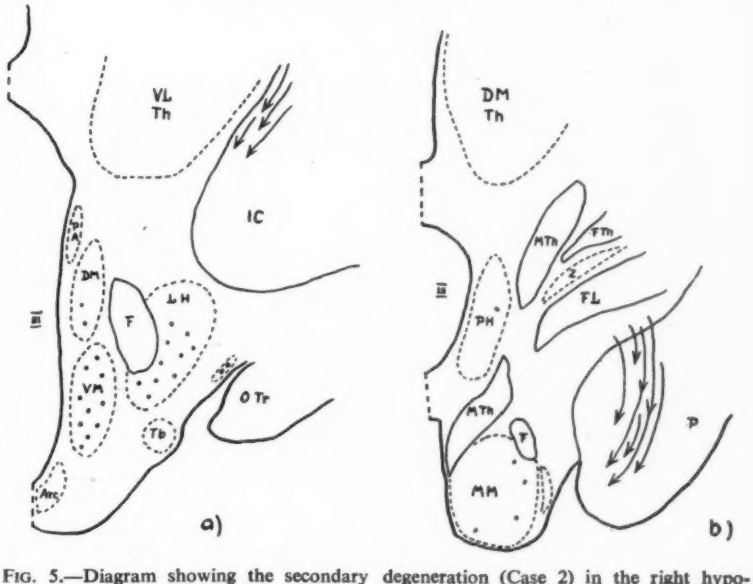

FIG. 5.—Diagram showing the secondary degeneration (Case 2) in the right hypothalamus (dotted areas.)

The course of the degenerated prefronto-pontine tract is indicated by arrows. (Compare Beck, 1950, Fig. 13, for its caudal course.)

* *In this and Fig. 2 the extent of the surgical lesion has been indicated by cross and single hatching according to its severity.*

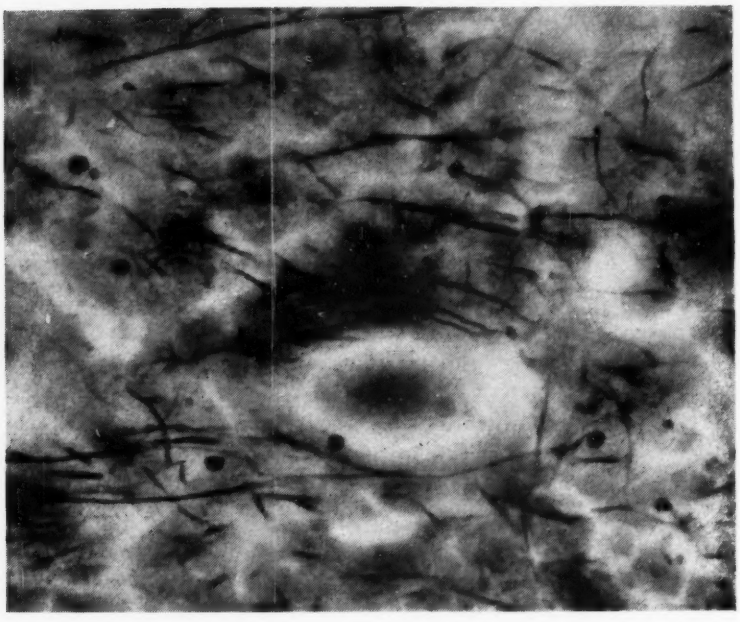

FIG. 6.—Numerous degenerated terminals (Case 1) in the dorso-medial nucleus of the thalamus. × 800.

FIG. 7.—Two degenerated terminals (Case 2) on a nerve cell in the ventromedial hypothalamic nucleus; the pericellular plexus has disappeared. × 1200.

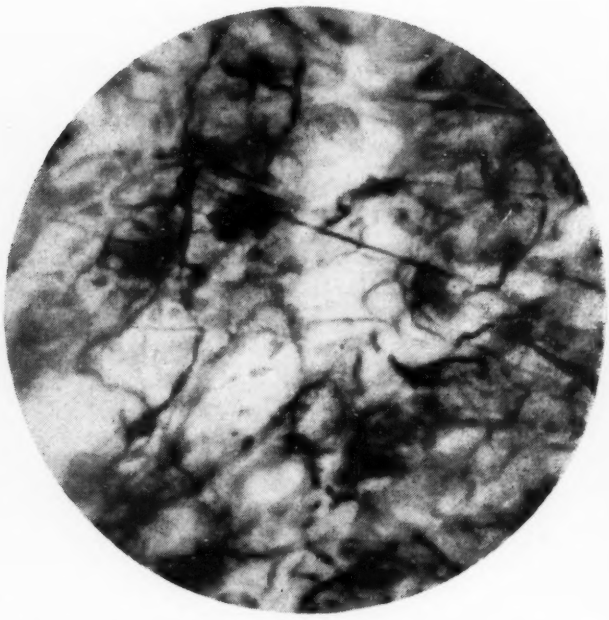

FIG. 8.—Severely degenerated fibres (Case 2) in the medial mammillary nucleus. × 1200.

All photomicrographs are taken from sections treated by the Glees' silver impregnation method.

FIG. 9.—Normal appearance of the fine-fibred (Case 1) prefronto-pontine fascicles; peduncular level. × 1000.

FIG. 10.—The same level in Case 2 as Fig. 9. The fascicles are completely degenerated, the fibres broken up and irregularly swollen. × 1000.

FIG. 11.—Normal fibre plexus (Case 1) around a pontine nerve cell in the immediate vicinity of the small medial fascicles. × 1300.

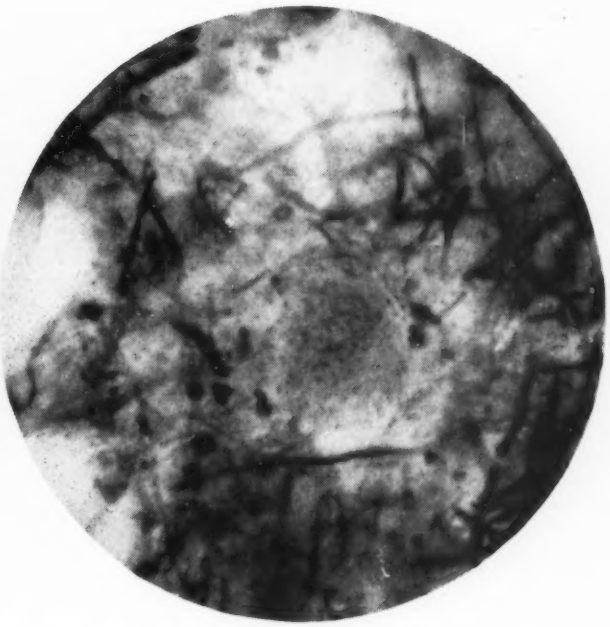

FIG. 12.—The same position (Case 2) as Fig. 11. Numerous degenerated terminals surrounding a pontine nerve cell. The fibre pattern is completely destroyed. × 1300.

degenerated, with its fascicles completely broken up both within the internal capsule adjacent to the nucleus ventralis lateralis and at the point where they descend into the cerebral peduncle. In the pons many degenerated terminals were seen surrounding the nerve cells in the immediate vicinity of small medial fascicles (Figs. 10 and 12). The ponto-cerebellar fibres were intact.*

The frontal cortex immediately posterior to the lesion showed degeneration in its dorsal and ventral aspects; laterally it appeared normal. Compared with Case 1 the degeneration was only slight, its distribution within the cortical layers similar.

There was no degeneration in the septal nuclei, the subthalamic nucleus, zona incerta, or Forel's fields H1 and H2.

The fasciculus cinguli and the superior longitudinal and uncinate fasciculi were degenerated; a detailed investigation of the long association tracts in this case will be included in a later publication.

Routine blocks showed early senile changes, including slight increase of lipofuscin and a few senile plaques. Only in the region of the hippocampus were these changes more pronounced and accompanied by Alzheimer's neurofibrillar change. We are satisfied that these slight senile changes did not obscure the effects of the leucotomy lesion.

Discussion

Perhaps the most interesting result of this investigation is the demonstration in the human brain of direct efferent fronto-hypothalamic pathways, arising well in front of the agranular frontal cortex, but not in the region of the frontal pole. The evidence seems to be strong. In Case 1, with its well defined topectomy of area 10/FE, all the hypothalamic nuclei, which were investigated in great detail, were free of terminal degeneration. On the other hand, in Case 2 where, in addition to the pole, adjacent parts of the orbital surface and dorsal convexity were involved, marked terminal degeneration occurred in the ventromedial and lateral hypothalamic nuclei, and to a lesser degree in the dorso-medial hypothalamic nucleus and the medial mammillary nucleus. Whether the hypothalamic degeneration was caused by the lesion of the medial orbital cortex (areas recta anterior and 11), or by the involvement of the cortex on the dorsal convexity, areas 9/FDm and anterior 8/FC, or by both combined cannot be ascertained from the present material.

There has been only one previous anatomical report describing direct fronto-hypothalamic connexions in the human brain, that of M. Meyer (1949) who, working in this department, demonstrated terminal degeneration in the mammillary body in leucotomized brains in which area 6/FB (and possibly anterior parts of 4/FA) were involved. More experience has been gained from experimental work in macaques. Ward and McCulloch (1947), by means of strychnine oscillography, " fired " the mammillary body and the lateral and posterior hypothalamic areas by stimulating area 6a; the supraoptic and paraventricular nuclei received impulses from more anterior frontal areas, while the paraventricular nucleus and the posterior hypothalamic area were fired from the medial and posterior orbital cortex. Le Gros Clark and Meyer (1950) have, so far, published only a summary of their frontal ablation experiments.* They state, however, that there is a massive projection from the agranular orbital cortex (mainly area 13) and also from area 6 upon the ventromedial hypothalamic nucleus which is bilateral, the contralateral fibres crossing in the rostrum of the corpus callosum. This agrees well with our human observations in which the ventromedial hypothalamic nucleus was the main site of terminal degeneration. Whether this connexion is bilateral also in the human brain cannot be ascertained from our Case 2 in which the primary surgical lesions in the two frontal lobes were symmetrical. Le Gros Clark and Meyer also noted degeneration in the dorso-medial hypothalamic nucleus, the anterior hypothalamic area, and the periventricular arcuate nucleus. Only the former showed slight terminal degeneration in our material. The lateral hypothalamic area which was severely degenerated in our material is not mentioned by Le Gros Clark and Meyer, who also, like ourselves, failed to find the degeneration in the supraoptic and paraventricular nuclei which was to be expected from the oscillographic results of Ward and McCulloch. Further anatomical investigations both in the human and monkey brain will be required to decide whether these discrepancies in detail are due to species differences, variation in site and extent of the primary lesion, or to accidental factors. In discussing the differences it should be remembered that area 13 and, indeed, the whole of the agranular orbital cortex, is relatively much smaller in man than in the monkey (Beck, 1949).

The orbito-hypothalamic fibres seem to run ventrally and possibly never enter the internal capsule. Degenerated fibres could be traced in our case from the ventromedial and lateral hypothalamic areas as far forward as the level of the anterior commissure. Here they were found in the region of the medial forebrain bundle and diagonal band

* While this paper was being written similar degeneration in the hypothalamus and in the prefronto-pontine tract has been confirmed in a second case of rostral leucotomy, with an almost identical primary lesion.

* Wall, Glees, and Fulton (1951), in a report published after the completion of this paper also emphasize the importance of the ventromedial hypothalamic nucleus as an end-station of orbital fibres in macaques.

below the commissure. It was presumably from this region that Sachs, Brendler, and Fulton (1949) observed strychnine spikes after stimulation of the posterior orbital gyrus of the monkey. Further anteriorly their course was somewhat doubtful, but Yakovlev, Hamlin, and Sweet (1950) described in normal myelin preparations fine fibres which they were able to follow from the " orbital limbus " through the putamino-caudate junction ventral to the anterior commissure into, among other regions, the lateral hypothalamic area. These fibres might be identical with those observed degenerated in the same region in our Case 2.

The existence of direct fronto-hypothalamic pathways is of considerable interest in view of the role which the posterior orbital cortex and the premotor region have been assumed to play in autonomic control. Delgado and Livingston (1948) showed that in monkeys and dogs stimulation of Walker's area 13 resulted in changes of respiration and blood pressure ; Livingston, Fulton, Delgado, Sachs, Brendler, and Davis (1948) extended these investigations to other autonomic functions, while Livingston, Chapman, Livingston, and Kraintz (1948) obtained a similar effect in the human brain stimulated before leucotomy. However, more recent observations have thrown some doubt on assigning considerable autonomic function to the orbital region in the human brain. Scoville (1949), and Scoville and his associates (1951) found neither autonomic disturbances nor the stereotyped restlessness, previously described by Ruch and Shenkin (1943), after very complete undercutting of the orbital cortex. Scoville's findings tally with observations made by one of us (Le Beau, unpublished) even after complete ablation of at least the medial two-thirds of the orbital cortex. Penfield and Rasmussen (1950) have likewise adopted a more critical attitude towards a major participation of the human cerebral cortex in controlling autonomic function. This aspect of the problem therefore also calls for further investigation.

The fronto-thalamic connexions will not be discussed here in detail. The subject has been dealt with exhaustively by Meyer (1949), and the findings in our second case are in complete agreement with her description. According to her classification this case would rank together with her Cases 3 and 4 as a purely " prefrontal " case, i.e., degeneration in the dorso-medial thalamic nucleus was slight and none of the other thalamic nuclei were affected. In our Case 1 the degeneration in the dorsomedial nucleus, although circumscribed and confined to a small focus in its antero-medial part was severe. Positive findings in this case, which was complicated by a vascular lesion, carry less weight than negative ones ; it is, however, at least possible to argue that in a case of ablation more fibres are involved than in leucotomy, particularly if one assumes that they may remain for some distance within the subcortical white matter before they converge in the centrum ovale. The integrity of the subcortical fibres has often been observed in our leucotomy material and has also been convincingly demonstrated by Sweet, Cotzias, Seed, and Yakovlev (1948). It thus seems possible that the prefronto-dorsomedial connexion is not as insignificant in the human brain as was deduced by Meyer (1949). These considerations equally apply to the short association fibres which were substantially degenerated in Case 1 and only negligibly affected in Case 2.

The remaining findings require only brief comment. Case 1 provides an elegant confirmation of the conclusion come to by one of us (Beck, 1950) that area 10/FE does not contribute to the prefronto-pontine tract.

Of the long association tracts only the superior longitudinal fasciculus showed mild degeneration. Degeneration of this system as well as of the fasciculus cinguli and the uncinate fasciculus has been described after prefrontal leucotomy in previous publications from this laboratory (Meyer and his associates, 1947, 1948). Recently the importance of their involvement has been stressed by Gruenthal (1950), Hassler (1950), and Yakovlev and others (1950), but so far this is not borne out in our material (Meyer and McLardy, 1948).

The septal nuclei were completely normal ; connexions from various frontal areas to these nuclei as described by Mettler (1947) and von Bonin and Green (1949) could not be confirmed.

Summary

Efferent connexions of the frontal pole have been studied by the Glees silver impregnation method in a case of topectomy of area 10/FE. The findings have been contrasted with a case of rostral leucotomy, aimed at undercutting areas 9/FDm and 10/FE.

Efferent fibre systems arising from the extreme frontal pole are very few. They are confined to a distinct projection upon the dorso-medial thalamic nucleus, some short association fibres to adjacent prefrontal cortex, a few callosal fibres, and a weak contribution to the superior longitudinal fasciculus. There is no connexion with the hypothalamus or any other subcortical centres.

A direct cortico-hypothalamic pathway has been demonstrated originating anterior to the agranular frontal cortex and terminating in the ventro-medial and lateral hypothalamic nuclei. Whether this tract arises from the medial orbital or dorsal frontal

cortex cannot be determined from the present material.

We are indebted to Dr. D. N. Parfitt who made available to us the pathological material and clinical data of Case 2, and to Miss Margaret Simms for technical assistance.

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ANOMALOUS HORIZONTAL LAMINATION OF NERVE CELLS IN THE SUPRAGRANULAR CORTEX OF AN IDIOT BRAIN

BY

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Except in the gross developmental anomalies, such as, for instance, microgyria, unequivocal signs of morphological immaturity in the cerebral cortex are not easily demonstrated.

Case Reports

Idiot Cortex.—The following case illustrates the findings in an idiot brain.

Case 1.—David M. was the only child of healthy parents of above the average intelligence, who were first cousins. There was no history of mental deficiency in the family. Delivery was by forceps three weeks before term, following an apparently normal pregnancy, and no obstetrical difficulties were encountered. An anaesthetic, thought to be chloroform, was given to the mother during the delivery. The child was slightly jaundiced during the first week of life, but there were no symptoms of cerebral irritation. His early progress was not satisfactory, and by the tenth day it was thought that he would be mentally deficient. At the age of 18 weeks he was admitted to King's College Hospital for investigation under Dr. Sheldon. Here he was found to have a small head, diameter 16½ in., and an "ugly M.D. look". Abnormalities were found on examination of the central nervous system. The pupils did not react to light, nor did the eyes follow a light. No attempt was made to grasp an object. There was nystagmus. The optic discs were rather pale. It was thought that hearing was present. The arms were very spastic, with large musculature, the tendon reflexes being very brisk and bilaterally equal. The legs were also very spastic, especially the right. The knee and ankle tendon reflexes were brisk and bilaterally equal, the plantar reflexes extensor.

The following tests were done at King's College Hospital: creatine excretion, 38 mg. in 24 hours; plasma cholesterol, 148 mg. %; creatine excretion, 47 mg. in 24 hours.

He was admitted to the Fountain Hospital as a mental defective at the age of 2¼ years, and died on April 25, 1949, within a fortnight of admission.

At necropsy the body was found to be that of a well-nourished male child. The head circumference was 17½ in.; the skull was long and narrow, with closed fontanelles. The meninges and cerebral venous sinuses appeared normal. The air passages were clear and the pleurae dry. Both lobes of the left lung were congested and heavy, with scattered patches of confluent bronchopneumonia. The right lung was congested. The gastrointestinal tract appeared normal. No abnormality was found in the endocrine system. There was a bilateral downward dislocation of the heads of the femora; the acetabula was imperfectly formed.

The unfixed brain weighed 282 g. The cerebral hemispheres were narrow in relation to their frontooccipital length, and were perceptibly firmer in consistency than normal. There was no microgyria. The corpus callosum was represented by a thin white membrane extending backwards for a distance of about 30 mm. from the site of the genu.

A detailed examination of the brain was made after it had been fixed in 10% formol saline. It was bilaterally symmetrical, and apart from the obvious narrowness of the cerebral hemispheres, of grossly normal proportions. The olfactory and other cranial nerves appeared normal. The dimensions of the cerebrum were: frontooccipital length 150 mm.; greatest breadth (mid-parietal) 100 mm.; greatest height 80 mm. The midbrain, pons, cerebellum, medulla, spinal cord, meninges, and cerebral vessels were of normal appearance.

From coronal sections made through the cerebrum at the level of the tip of the caudate nuclei (Fig. 1),

FIG. 1.—Coronal section of brain at level tip of caudate nuclei.

through the parietal region just posterior to the basal ganglia and through the occipital lobe, it could be seen that there was a generalized and symmetrical dilation of the lateral ventricles. The choroid plexuses appeared normal. Associated with the internal hydrocephalus there was a gross deficiency in the amount of central white matter, of about the same degree throughout. The extreme thinness of the corpus callosum was also apparent. In the depths of the sulci the cortical grey matter was separated from the lateral ventricle by a distance of about 4 mm., each gyrus possessing a central core of white matter of about the same width. In the central core of many of the gyri, and particularly at the confluence of two or more, the white matter contained small, pinkish-grey zones in which minute blood vessels could be seen with the naked eye.

The central block, containing the basal ganglia, was divided sagittally. The appearances on either side were identical. The interventricular foramina were abnormally wide, being 7 mm. in diameter. The third ventricle was moderately dilated, the lamina terminalis being of paper thinness. On the other hand, the aqueduct of the midbrain did not appear to be dilated, with a diameter of 1 mm. The fourth ventricle was of normal appearance, and the lateral recesses were patent. The thalamus was small, with an antero-posterior length of 18 mm. There was no anterior tubercle, this accounting in part for the abnormal width of the interventricular foramen. There was no massa intermedia. The relatively small size of the thalamus resulted in some distortion and foreshortening of the hind part of the third ventricle, the hypothalamic sulcus running at an angle of 45° to the horizontal. The septum lucidum was extremely thin, and the fornix system could not be identified, while the mammillary body was small and inconspicuous. On the other hand, the projection of the caudate nucleus into the lateral ventricle appeared to be of normal size in relation to the size of the brain.

Frozen sections were cut from blocks from the superior, orbital, and lateral parts of the left frontal lobe. Blocks for celloidin embedding were also taken from the frontal, temporal, parietal, central, and occipital parts of the right cerebral hemisphere, and from the right basal ganglia, brain stem, pons, medulla, cerebellum, and spinal cord. The frozen sections were stained by all the usual histological methods, the celloidin sections by Nissl's, Heidenhain's myelin, and Holzer's glial fibre methods.

The most unusual feature of this brain was the presence of a cytoarchitectural anomaly in the outer layers of the cerebral cortex, which was most conspicuous in the superior frontal region. In place of their normal, poorly defined radial arrangement, the cells of the second and third cortical layers were distributed in rows of single cells running parallel with the surface of the brain (Figs. 2 and 3). The nerve cells themselves showed signs of immaturity, having rather scanty cytoplasm which contained very little Nissl substance, and were in many instances bipolar, in this respect morphologically resembling neuroblasts. With the exception of radial fibres in the deeper layers, there were very few myelinated fibres in the cortex. A similar

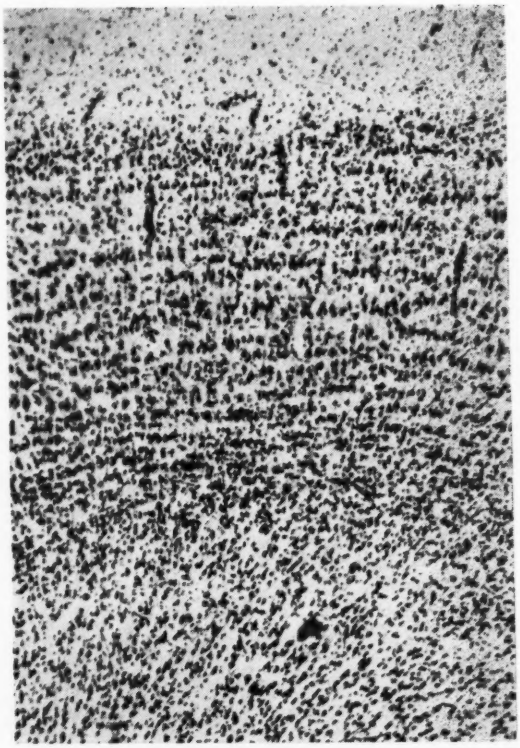

FIG. 2.—Cortex of superior frontal gyrus. Nissl. × 50.
FIG. 3.—Same as Fig. 2. × 14·5.

sparseness of neurofibrils was seen in silver preparations. No fibres appeared to run horizontally between the rows of cells in the outer layers. Although most conspicuous in the prefrontal cortex, the anomalous arrangement of nerve cells was not entirely confined to this part. Except in the central region, a tendency to horizontal lamination, particularly in the outer margin of the second layer, could be detected in all regions of the neocortex. In addition, the first cortical layer was unusually wide throughout, containing large Cajal nerve cells which lay, in some instances, in abnormal positions. A peculiar arrangement of cells was found also in the palaeocortex, where the dentate gyrus was reduplicated, consisting of two closely apposed parallel rows of cells, the outer row being less regular than the inner. In the pyramidal cell layer of the cornu Ammonis the normal crowding of cells in its inner part was absent. No abnormality was noted in the entorhinal cortex.

Immediately beneath the ependyma of both hemispheres there was a narrow zone of dense glial fibrosis, containing relatively few astrocytic nuclei. Subependymal gliosis was also found in the wall of the third ventricle. Contrasting with this there was a densely cellular zone occupying the greater part of the thickness of the shrunken central white matter, containing an excess of astrocytes and oligodendroglial cells and occasional microglial cells, which was the site of a fine glial fibrosis. This zone also contained a large number of neuroblasts scattered throughout the affected white matter. The blood vessels in the central zone, although not structurally altered, were more numerous than in the normal and appeared to be widely dilated. There was no perivascular inflammatory reaction.

There were very few poorly myelinated fibres immediately beneath the ependyma, in the zone corresponding to that in which there was the most dense glial fibrosis. Elsewhere throughout the central white matter, except in the U-fibre systems, myelination was scanty, the myelinated fibres tending to run in poorly defined stripes parallel to the ventricle (Fig. 4). The fibres in the deep white matter of the frontal lobe tended to run together in a diffuse bundle, or in a series of concentric lamellae, apparently contributing fibres to the majority of the superjacent gyri. Posteriorly this system of fibres appeared to be continuous with the external capsule. In the central region the central cores of the gyri were more completely myelinated than elsewhere. The individual myelin sheaths were not apparently abnormal, and there was no indication of recent myelin breakdown. The histological findings seemed to suggest that incomplete myelination had occurred, rather than that there had been a true demyelination.

Significant findings elsewhere in the brain may be mentioned briefly. Irregular myelination had occurred in the thalamus, particularly in the dorsomedial nucleus, with the production of an abortive status marmoratus. In the myelin picture, the anterior, dorsomedial and lateral nuclear groups could be easily identified, although in Nissl preparations the definition of these nuclei was less clear, probably owing to the presence of the status marmoratus and widespread fine and coarse glial fibrosis. The internal capsule, crura, and pyramidal tracts, although well myelinated, were disproportionately small, and there was considerable glial fibrosis in the capsule externa and extrema. No abnormality was seen in the cerebellum, the external granular layer of the cortex having disappeared, nor in the leptomeninges, meningeal and intracerebral blood vessels and choroid plexuses. No other anatomical anomalies were noted.

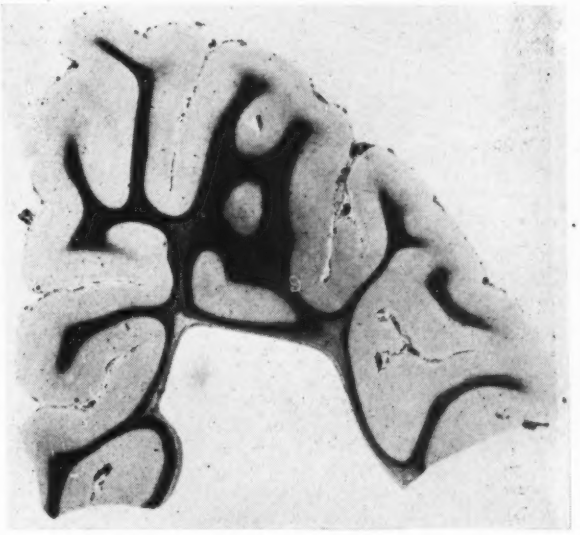

FIG. 4.—Coronal section through parietal region. Heidenhain's myelin method. × 1·9.

The Prenatal Cortex.—It has been possible to make a comparison between the idiot cortex and that of a premature infant.

Case 2.—This child was born after 26 weeks' gestation, weighed 678 g., and lived for five days. The brain weighed 103 g. Apart from a small recent haemorrhage into the body of the left caudate nucleus, the brain was not structurally abnormal. The extent of development of the cerebral sulci corresponded fairly well with that shown by Connolly (1940) in a cerebral hemisphere of this age.

It can be seen in Fig. 5 that there is a comparable horizontal lamination of cells in the outer two-thirds of the cortex, although this is not so obvious as in the idiot brain. In the latter the cells are considerably more widely spaced, the distance between the rows being increased in consequence. Also, the primitive arrangement of cells in vertical columns persists more markedly in the late foetal brain. The tendency to horizontal lamination in this brain, as in the idiot's, was more noticeable in the prefrontal region of the cortex than elsewhere.

Discussion

I was unable to find any description of a lamination of nerve cells resembling that seen in the cortex of the $2\frac{1}{4}$ year old idiot in the literature on cortical maldevelopment or on foetal and infantile lesions. Neither is it recorded in the literature

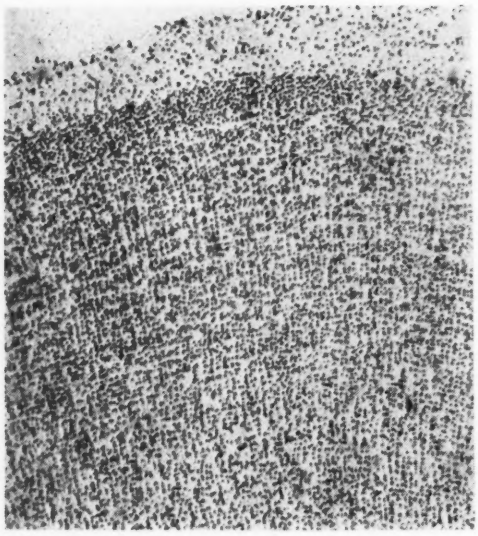

FIG. 5.—Frontal cortex of premature infant. Nissl. × 80.

on hydrocephalus, and Professor D. S. Russell (personal communication), who was shown the slides of this case, has seen nothing resembling it in her material.

Our knowledge of the morphological aspects of the later stages of prenatal cortical development is surprisingly fragmentary. Following the work of His (1890), studies have been made more recently by Filimonoff (1929) and Fitz-Gerald (1940). None of these authors describes horizontal lamination in the cortex, nor does Conel (1939) in his study of the neonatal cortex. It is, however, apparent from photographs presented by both Filimonoff and Fitz-Gerald that irregular horizontal layers of neuroblasts may be formed at a time when they are presumably migrating through the cerebral hemisphere. In Filimonoff's photographs of the calcarine region in a $3\frac{1}{4}$ months old human foetus such an appearance is shown in the inner dark layer intervening between the pale *Zwischenschicht* and the densely cellular subependymal matrix, as well as in the diffuse layer of cells immediately beneath the definitive cortex. One of Fitz-Gerald's photographs also shows a horizontal lamination of cells immediately beneath the definitive cortex of a 95 mm. human embryo.

The finding of horizontal lamination of cells in the cortex of an immature child of about 26 weeks' gestation, as in the second case described, is therefore of considerable interest as it seems to provide a clue to the interpretation of the cortical anomaly in the first case. The persistence of this arrangement in the latter, exaggerated by the subsequent increase in depth of the cortex, appears to suggest that a check had occurred to the normal process of cerebral maturation, presumably during the prenatal period. However, with regard to the occurrence of horizontal cell lamination as a mark of immaturity, a comparative study of the cortex at birth in a large series of brains would be necessary in order to assess the degree of individual variability of maturation that may be found before evidence of this kind can be of much value in precisely dating the incidence of a damaging lesion. It should be noted that the lamination in the idiot brain is clearly confined to the upper layers of the cortex, thereby providing an example of the much disputed abnormality in the supragranular cortex in such cases (Bolton, 1914; Stewart, 1935; Norman, 1938).

From the histological study of the white matter lesion alone, no definite opinion could be expressed as to the nature of the damage which it has evidently sustained. Marked internal hydrocephalus was present, the dilation being confined to the third and lateral ventricles, although there was no expansion of the brain as a whole, or of the skull. The possibility that there had been a transient increase in the intraventricular fluid pressure produced by an obstruction either to the circulation of cerebrospinal fluid or to the venous drainage of the choroid plexus cannot be ruled out. On the other hand the hydrocephalus may equally well have occurred *ex vacuo* as a consequence of the white matter shrinking after damage of an anoxic nature. The presence of what appears to be an abortive marbling in the thalamus would support an anoxic pathogenesis. Although status marmoratus of the subcortical centres is usually due to trauma sustained at birth (Norman, 1949), this does not wholly preclude its occasional onset in prenatal life (Meyer and Cook, 1936).

Whatever the pathological explanation of this lesion may be, it is probable that the cortical anomaly arose as a sequel to the white matter damage, or as part of the same process. The concentric arrangement of myelinated fibres around the ventricles invites comparison with the concentric demyelination described by Baló (1928). It was suggested by Spatz (1931) and by Hallervorden and Spatz (1933) that this marks the site of periodic precipitations accompanying the diffusion of a toxic substance through the white matter. In the present instance one might suppose that a similar diffusion had occurred from the ventricles through the ependyma into the deep cerebral white matter, which as yet had not become fully myelinated.

Summary

The brain of a spastic idiot child aged $2\frac{1}{4}$ years is described. Anomalous horizontal lamination of nerve cells was seen in the supragranular cerebral cortex, particularly marked in the prefrontal region, associated with the presence of internal hydro-

cephalus and widespread shrinkage and gliosis through the imperfectly myelinated white matter of both cerebral hemispheres. A comparable, although less conspicuous, laminar arrangement of cells was seen in the prefrontal cortex of the brain of a premature infant.

I am grateful to Professor Alfred Meyer for his advice and help in interpreting the histological picture in the idiot brain, to Dr. L. T. Hilliard for providing access to the Fountain Hospital case records, and to Elisabeth Beck for the photographs (except Figs. 1 and 5); also to Dr. R. M. Norman for his interest in the case, and to Dr. R. Aidin of Southmead Hospital, Bristol, for providing the premature brain.

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BRAIN ABSCESS: ASPIRATION, DRAINAGE, OR EXCISION?

BY

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In treating brain abscess we have three primary concerns: saving life, preserving or restoring function, and preventing sequels such as epilepsy and recurrence of infection. Our success with the first of these is accurately expressed by the immediate mortality rate, but information about the last two can only be obtained by long-term follow-up studies. And for statistical assessment larger figures are required than any one clinic can supply. Furthermore, the methods of treatment tend to differ in different clinics. In Oxford, for instance, we have records of about 120 cases of brain abscess treated since 1938, but most of these have been dealt with by excision after successful aspiration, and we have little useful information about aspiration or other forms of drainage as the sole procedure. Accordingly we approached Professors Norman Dott and Sir Geoffrey Jefferson who kindly placed at our disposal the records of their cases treated in Edinburgh and Manchester over the last 25 years or so. From the three centres there were altogether 295 cases. Of these patients, 118 died soon after operation (40%). The remaining 177 patients survived for periods up to 26 years, and of these it has been possible to obtain adequate follow-up information in 173 cases. As we were particularly interested in the long-term results, we have not included any cases treated within the last 12 months.

We found that in general three methods of treatment had been used (Table I): aspiration (with or without a decompression); continuous drainage by a tube, or by marsupializing the abscess; and excision (with or without previous aspiration and/or decompression).

No clinic had applied any of these methods to the exclusion of others, but there was a strong preference for excision in one clinic, and for continuous drainage in another. In the third clinic there was less rigidity and the various methods all had a fair trial.

TABLE I
METHODS OF TREATMENT

Method	No. of Cases	Died	Mortality (%)
I. Aspiration (with or without decompression)	95	58	61
II. Drainage (by tube, fungus, or marsupialization)	89	45	50
III. Excision (with or without previous aspiration and/or decompression)	111	15	13
Total	295	118	40

Mortality

The mortality rates of the different methods (Table I) are not comparable, for in many of the cases finally treated by excision the abscess had already been tided over to the chronic stage by repeated aspirations; at the time of the excision an apparent cure had already been effected and the patient was often free from symptoms, although papilloedema or other signs persisted. In addition, many of the cases treated by aspiration alone were desperate ones, and the aspiration was done when the patient was *in extremis*.

Another factor which must be considered is the introduction of penicillin, which is given systemically, injected directly into the abscess cavity, and also into the cerebrospinal fluid pathways if there is risk of meningitis. There is no doubt that all of us have much more confidence in the treatment of brain abscess now than at any time in the past, and we are inclined to ascribe this largely to penicillin. From our survey this would appear to be the case, for if the material is divided into pre- and post-penicillin groups, the mortality rate in the former

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was 53% and in the latter 27% (Table II). Improved results from the use of penicillin were especially striking in the cerebellar abscesses and in the bronchogenic abscesses of the cerebral hemisphere. In one centre, among 21 cases of cerebellar abscess, 10 were operated on without penicillin, and there were seven deaths (70%), whereas in 11 cases operated on with the aid of penicillin there was only one death (9%). In the same centre the mortality from bronchogenic abscesses was 100% before and 32% after the introduction of penicillin. On the other hand, in the common type of abscess of the cerebral hemisphere, penicillin did not produce much change in the results : of 100 cases of abscess of the cerebral hemisphere, 44 were treated without penicillin and there were 16 deaths (36%), while 56 were treated with penicillin with 17 deaths (30%).

We next sought to see what effect penicillin had had on the various methods of treatment. The figures (Table III) show that penicillin has produced considerable improvement in the results of all methods of treatment. The two determining factors in the use of antibiotics are the sensitivity of the organism to the antibiotic, and the possibility of treating the whole of the infected area with it. As to the former, of 100 cases of cerebral abscess in Oxford, organisms were found in smears or on culture in 75, and in 12 of these the organisms were of a type insensitive to penicillin. In the whole series streptomycin was only rarely used ; some of the penicillin-resistant organisms may prove sensitive to this and other antibiotics in the future.

The second point about the access of penicillin to the infected area is concerned with the character of the abscess, i.e. whether it is a single cavity or has multiple loculi, or whether there are multiple discrete abscesses. In this connexion it will be seen later that the abscess is strictly unilocular in rather less than half the cases, and in the remainder it is possible that the penicillin is getting to only one of the loculi.

TABLE II

INFLUENCE OF PENICILLIN ON TREATMENT OF BRAIN ABSCESS

	No. of Cases	Died	Mortality (%)
Without penicillin	145	77	53
With penicillin ..	150	41	27

TABLE III

METHODS OF TREATMENT

	No. of Cases	Died	Mortality (%)
Aspiration :			
Without penicillin ..	50	37	74
With penicillin.. ..	45	21	47
Drainage :			
Without penicillin ..	57	32	56
With penicillin.. ..	32	14	41
Excision :			
Without penicillin ..	38	8	21
With penicillin.. ..	73	7	9
Total	295	118	

Preservation and Restoration of Function

In general it would appear that the chances of improving a neurological disturbance are rather better with aspiration than with excision. This is well seen in the case of the visual field defect in temporal lobe abscess : after aspiration it is by no means uncommon for the hemianopia to clear up completely, whereas with excision the upper quadrant defect may be rendered permanent, and in some cases a pre-operative upper quadrant defect has been converted into a complete and permanent hemianopia. On the other hand, we have not seen a case in which aphasia has been made any worse by excision of a left temporal abscess, and in most cases it has cleared up completely. With excision the risks of damage are less in the chronic than in the acute stage before encapsulation.

Whichever method of treatment is used, the result will depend largely on how much of the disability is due to destruction by the abscess and how much is due to local pressure effects. Of 175 patients in this series who recovered from a brain abscess and were followed up, 8% were disabled by profound motor, sensory, or visual defects ; another 8% had slight defects but were able to maintain themselves in gainful occupations ; the remainder had no significant neurological disturbance.

Late Complications

The sequels with which we have been particularly concerned are recurrence of the infection and epilepsy.

Recurrence of Infection.—Among the 96 survivors of excision in this series there was no case in which an abscess recurred at the same site once it had been excised. We are, however, informed that Professor Cairns and Mr. Falconer had a case at the Military Hospital for Head Injuries, Oxford, in which a temporal abscess recurred several months after it was removed. Recurrence in this case was

thought to be due to a fresh infection from the mastoid which had not been adequately treated.

With aspiration or drainage the risk of recurrence is greater. Of the 88 patients treated by these methods who left hospital alive, seven subsequently developed recurrent infection at the same site, at intervals varying from three months to 13 years, and all of these died. Expressed statistically the risks are thus not very great (8%), but should be borne in mind. The efficacy of any aspiration or drainage procedure depends largely on the character of the abscess, that is, whether it is a single or multilocular cavity. In 91 cases of which we have surgical or necropsy material at Oxford, the abscess was multilocular (Table IV) in 39 (43%). It may be that penicillin instilled into one loculus permeates adjacent loculi to some extent, but in two cases of multilocular abscess removed at operation only the loculus treated with instillation of penicillin had been sterilized.

Epilepsy.—The practical functional result after abscess of the cerebral hemisphere is often determined by the presence or absence of epilepsy. Epilepsy is a frequent feature of the development of an abscess, occurring before operation in 27% of the 264 cases of abscess of the cerebral hemisphere in this series. The incidence corresponds fairly closely to that in cases of neoplasm.* After treatment of the abscess epilepsy was manifest in 72 cases among the 152 survivors who have been followed up : that is to say, 47% of the survivors of abscess of the cerebral hemisphere subsequently had fits. McKenzie (1948) reported an incidence of 30·5% in 47 survivors out of 105 cases. Our figures of post-operative epilepsy approximate to the incidence of post-traumatic epilepsy in cases of penetrating missile wounds of the brain reported by Ascroft (1941), 45%, and by Russell (1951), 43%.

The incidence of post-operative epilepsy relative to the method of treatment is seen in Table V, from which it would appear that there is little difference whether the abscess capsule is left in the brain or is primarily or secondarily excised. However, when the different parts of the cerebral hemisphere are considered separately (Table VI), although the figures are small, it is seen that epilepsy following treatment of frontal abscess is considerably more common after aspiration or drainage than after excision.

The following additional factors in the incidence of epilepsy have been considered.

* Hoefer, Schlesinger, and Pennes (1947) reported epilepsy in 36% of 476 cases of intracranial tumour, and Penfield and Erickson (1941) in 37% of 703 cases.

TABLE IV

RELATIVE INCIDENCE OF UNILOCULAR, MULTILOCULAR, AND MULTIPLE BRAIN ABSCESSES

Nature of Abscess	Site of Lesion		No. of Cases	%
	Cerebral	Cerebellar		
Unilocular ..	35	9	44	48
Multilocular ..	34	5	39	43
Multiple ..	8	—	8	9
Total ..	77	14	91	

TABLE V

POST-OPERATIVE EPILEPSY IN VARIOUS METHODS OF TREATMENT

Method	No. of Cases Followed Up	Epilepsy	%
Aspiration	31	15	48
Drainage	38	21	55
Excision :			
(*a*) Without previous aspiration or decompression	18	10	55
(*b*) With previous aspiration or decompression	65	26	40

Age.—Table VII shows that there was no significant difference in the incidence of epilepsy in any particular age group ; children seem to be no more or less liable to post-operative epilepsy than adults.

Time of Onset of Epilepsy after Treatment.—Fits frequently occurred within a few weeks of operation but in one case the interval was 14 years. In 63% of the cases of post-operative epilepsy the first fit came on within 12 months of operation. However, after frontal abscess the onset of epilepsy was delayed : only 10 of the 27 patients had their first fit within the first year. With abscesses of other sites 70 to 100% of those having post-operative fits had them within a year of operation.

Influence of Penicillin.—Table VIII shows that the incidence of epilepsy was 57% among cases treated without penicillin and 40% among cases treated with penicillin. These figures must be viewed with caution since the incidence of epilepsy after missile wounds in Ascroft's series (45%), none of which had penicillin, did not differ from the incidence in Russell's series (43%), most of which were treated with penicillin.

TABLE VI

INCIDENCE OF POST-OPERATIVE EPILEPSY IN RELATION TO SITE OF ABSCESS

Site of Abscess	Mode of Treatment	No. of Cases	Incidence of Post-operative Fits	%
Frontal lobes	Aspiration or drainage	18	13	72
	Excision	32	14	44
Temporal lobes	Aspiration or drainage	30	12	40
	Excision	26	7	27
Parietal lobes	Aspiration or drainage	5	2	—
	Excision	11	6	—
Occipital lobes	Aspiration or drainage	5	2	—
	Excision	5	3	—
Multilobular and multiple abscesses	Aspiration or drainage	11	7	—
	Excision	9	6	—
Total		152	72	—

TABLE VII

INFLUENCE OF AGE ON INCIDENCE OF EPILEPSY AFTER OPERATION FOR BRAIN ABSCESS

Age Group	No. of Cases	Incidence of Fits	%
A. (1–10 years)	28	12	43
B. (11–20 years)	34	15	44
C. (21–30 years)	46	25	54
D. (31–40 years)	15	8	53
E. (40 and over)	29	12	41
Total	152	72	

TABLE VIII

INFLUENCE OF PENICILLIN ON INCIDENCE OF EPILEPSY

Cases Treated	No.	Incidence of Fits	%
Without penicillin	61	35	57
With penicillin	91	37	40
Total	152	72	

The Use of Thorotrast.—It is believed by some that the use of thorotrast for pyography during the treatment of brain abscess increases the risk of epilepsy. We have not two comparable series, but in one centre there were 50 patients in whom thorotrast was used, and of these 23 subsequently had fits, and 27 had no fits. That is to say, the incidence of epilepsy was no higher in this thorotrast group than in the whole post-operative series.

The Use of Anticonvulsants.—There is abundant evidence that patients with cerebral abscess, however treated, should remain on an anticonvulsant régime for several years, if not permanently. We have on many occasions seen patients whose fits have been controlled by phenobarbitone for two or three years, to the point where they felt justified in discontinuing the drug, and this has been followed immediately by a recurrence of seizures, which were controlled again by resuming the drug. There is no evidence that phenobarbitone in ordinary therapeutic dosages exerts any harmful effects on the patient's well-being or general health, and although we realize that in advising it for all patients some will be having it unnecessarily, there is no way of selecting the patients except by waiting to see whether or not they have a fit. Some authorities (Russell, 1950) prefer not to give phenobarbitone until fits develop, but in one case in this series the first manifestation of post-operative epilepsy was status epilepticus which proved fatal, and this patient had had no prophylactic anticonvulsant treatment.

Whatever method of treatment is employed, post-operative epilepsy remains a hazard in brain abscess, and it has accounted for death in status epilepticus in five of the 152 survivors in this series whose subsequent fate is known. These were all cases of frontal abscess, two of which had been treated by excision, two by tube drainage, and one by aspiration. This corresponds with the findings of Whitty (1951) that it is with frontal lesions in particular that status epilepticus is apt to arise.

In four of the 72 patients with post-operative epilepsy the attacks were so frequent, despite treatment, that the patient was virtually disabled

by them. On the other hand, in 61 cases the fits were so mild and infrequent as not to constitute a serious disability, although the fact of epilepsy sometimes demanded a change in occupation. In only 12 cases (16% of the total with post-operative epilepsy) was it considered necessary to supplement phenobarbitone with other anticonvulsants. As the patients are followed over a period of years, the frequency and severity of the attacks tend to diminish. When this does not happen, and epilepsy constitutes a disability, the possibility of surgical excision of an epileptogenic focus should be considered. In cases of epilepsy associated with hemiplegia and disorders of behaviour the question of hemispherectomy should be reviewed in the light of Krynauw's recent work (1950).

Discussion

As regards death rate, our results do not differ significantly from those published in a collective review by Webster and Gurdjian (1950) who found that the average mortality for aspiration was 50% ; for tube drainage procedures, 50% ; and for excision, 12%. Even apart from the mortality rate, we interpret our figures for post-operative epilepsy and recurrence of abscess as indicating that of the methods which have been tried, excision is by a slight margin the most reliable. The risks of relying on aspiration derive from the fact that many abscesses are multilocular, and it may not be possible to deal with all of the loculi by aspiration. The same risk is incurred in tube drainage. It is a fact that many patients treated by aspiration will improve clinically, although the abscess continues to expand, as is shown in serial pyograms, which we regard as an essential part in the management of these cases. There is also the risk, albeit slight, of a late recurrence of the infection in the capsule of an abscess left in the brain when treatment has been by aspiration or tube drainage. This risk is particularly marked in chronic brain abscess after a penetrating missile wound.

The addition of penicillin instillation to aspiration or other drainage techniques is an improvement, but there remain the infections due to insensitive organisms, and the difficulty of sterilizing a multilocular abscess.

We have found no significant difference in the incidence of epilepsy whether the abscess be excised or treated by aspiration, though in abscesses of the frontal lobe the results suggest that the risk of epilepsy is greater if the abscess is not removed. The advantages of aspiration are its simplicity, and the fact that it carries slightly less risk of adding to a neurological deficit than does excision. These are important considerations, especially in the Rolandic region or in the speech area, and doubtless more cases will be treated by aspiration as time goes on. If so, we would urge that a strict test of cure be applied before the patient is discharged : that he should be free from symptoms and signs of increased intracranial pressure ; that the cerebrospinal fluid should have reverted to normal ; that the thorotrast-encrusted abscess should have shrivelled up, as seen in serial pyograms ; and that if there is any doubt at all, a ventriculogram should have shown that there are no residual loculi.

In conclusion, it must be emphasized that no hard and fast rules can be laid down in advance. Each case must be treated on its merits. In some cases with high intracranial pressure, operative decompression is necessary to save life, and in these it is usually advisable at a later stage, or even at the time of the first operation, to excise the abscess. In other cases, where the abscess is situated in an eloquent area of the brain and the abscess is unilocular, repeated aspiration is the better method of treatment. But in these regions, as in other parts, an abscess is occasionally encountered which does not collapse after repeated aspiration, and must be excised to obtain a cure.

Summary

A group of 295 cases of brain abscess from Edinburgh, Manchester, and Oxford has been reviewed. Of the 177 survivors, 173 have been followed for periods of one to 26 years.

In general, three methods of treatment were followed : aspiration (95 cases, with mortality of 61%) ; tube drainage (89 cases, with mortality of 50%) ; and excision (111 cases with mortality of 13%). The overall mortality was 40%.

The mortality rate without penicillin was 53%, and with penicillin 27%.

The risk of adding to certain neurological deficits, for example, visual field defects, was less with aspiration than with excision.

The recurrence rate after aspiration or drainage was 8%. After excision there was no recurrence among 96 survivors.

Post-operative epilepsy was manifest in 72 cases among 152 survivors of abscess of the cerebral hemisphere. Of these, five (all of them frontal lobe cases) died in status epilepticus. In 63% of patients with post-operative fits the first fit occurred within 12 months of operation.

The incidence of post-operative epilepsy in frontal lobe abscess was considerably higher after aspiration or drainage than after excision.

The findings in this series are slightly in favour of excision as the best method of treatment but each case must be treated on its merits.

The value of regular and indefinitely prolonged anticonvulsant therapy after operation for brain abscess is stressed.

We are indebted to Professor Norman Dott, of the Royal Infirmary, Edinburgh, for allowing us to include his material in this paper, and to the secretarial staff of his Department for all their help.

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THE DIFFUSION OF SUBSTANCES IN THE SUBARACHNOID SPACES*

BY

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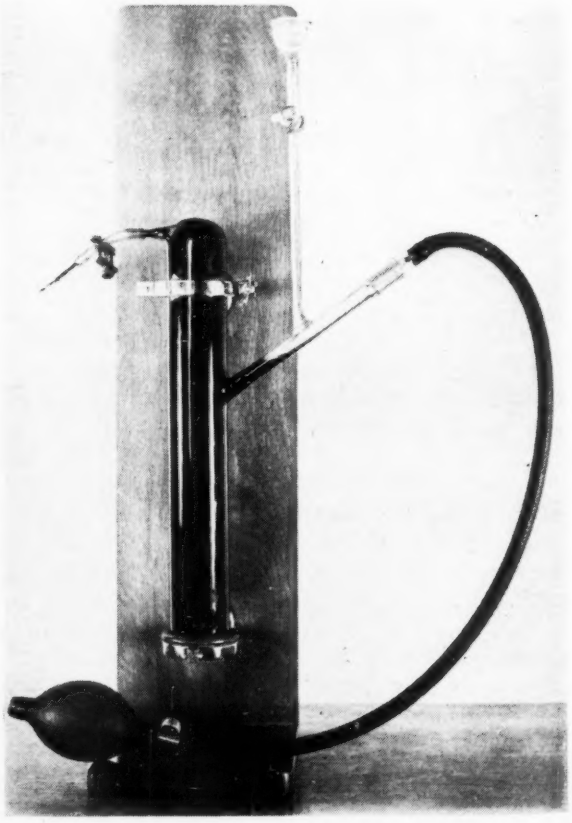
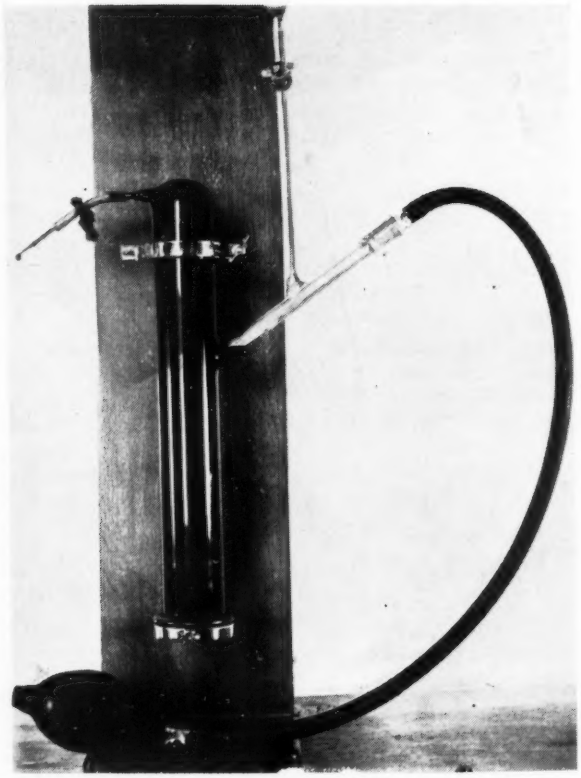
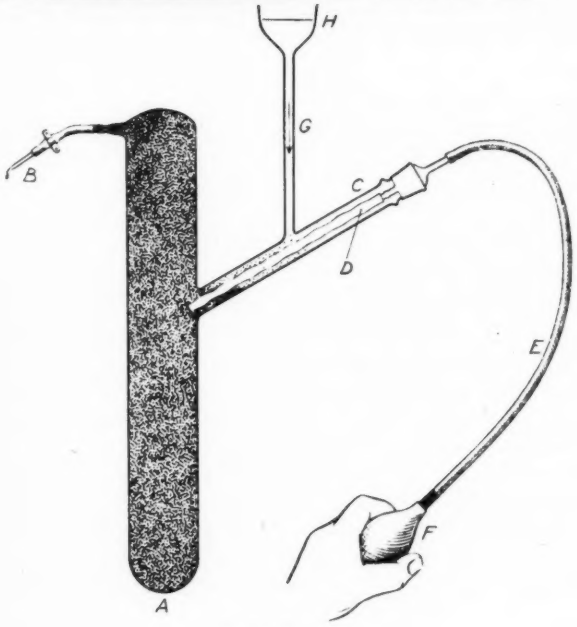
The diffusion of particulate suspensions introduced into the subarachnoid spaces has been studied by several authors after Quincke. Among the most noteworthy contributions to the subject are some recent papers of Brierley. In the last of these papers Brierley (1950) has shown that particles of indian ink, suspended in saline, and introduced into the cisterna magna of the rabbit (using an adequate technique in order to avoid any modification of the pressure of the cerebrospinal fluid) are arrested at the medial border of the spinal ganglion. Here he suggests the presence of an arachnoid " cul de sac " and not of a fissure, as claimed by Hassin. This cul de sac, according to Brierley, would open into the periradicular spaces.

Brierley showed that as far as the brain is concerned, indian ink particles would accumulate 24 to 48 hours after the injection in the perivascular spaces, particularly in the hippocampal region. Brierley claims that these findings conflict with the generally accepted opinion of Weed (1914), Schaltenbrand and Bailey (1927), and Kubie (1928), who support the view of an outward movement of the perivascular fluid from the perivascular to the subarachnoid spaces ; and Brierley, in the absence of passive transport of the particles by phagocytes, declares that he himself is at a loss to explain these findings. But the views of Weed, Schaltenbrand, and Kubie that the subarachnoid system would represent a large lymphatic space, where the lymph, coming from the Virchow-Robin spaces, is diluted into the fluid secreted by the choroid plexuses, and finally reabsorbed into the large venous sinuses through the arachnoid villi, are well supported by clinical findings (Belloni, 1949). It will be shown in the present paper that Brierley's findings do not conflict with the latter views, and can be explained, if we take into account that the hydraulic conditions of the cerebrospinal fluid and of the perivascular lymph *are not static*, but, instead, are continually subjected to pressure variations due to the pulsations of the vascular system. Such pressure variations must give rise to counter-currents in the perivascular fluid which might send up, against the stream, as it were, along the perivascular spaces, substances introduced in the subarachnoid system, in spite of the existence of a basal, slow, and most probably intermittent, lymphatic flow in the opposite direction.



* A preliminary communication was given at a meeting of the Società Italiana di Neurologia at the Veneto-Emiliana branch on October 25, 1950.





FIGS 2 and 3

To test such a hypothesis, the model shown in Figs. 1, 2, and 3 was used. The 400 ml. vessel A is filled with an indian ink suspension from the funnel H, after which water is allowed to run in, always from H, until all the side tubes G and C have been completely freed from indian ink ; at this moment tube B is closed.

Under these conditions it was found that in 24 to 48 hours the indian ink had diffused from A up the tube C for a distance of 3 to 4 cm. (Fig. 1).

Then, if the outlet tube B is partially opened so that 3 or 4 drops run out per minute (the fluid level in H being kept practically constant by adding from time to time some tap water), it will be found that not only does the diffusion of the indian ink up the tube C progress no further, but that, on the contrary, the indian ink, which had already diffused, is slowly pushed back from C towards vessel A until the limit between the water and suspension reaches the final constant level shown in Fig. 2.

It appears therefore that this very slow stream of water from H into A is sufficient to oppose the diffusion of indian ink into the fluid contained in C.

While this inlet stream of water is being continued, the rubber balloon F is rythmically compressed so that the closed end rubber tube D (which is in connexion with the balloon) will rythmically pulsate in order to imitate the pulsation of an artery. It will then be found that, as a result, diffusion of indian ink will immediately begin in C into the clear fluid which surrounds the rubber tube D and which may be taken to represent a perivascular space (Fig. 3).

It is clear therefore that Brierley's findings, i.e. the diffusion of indian ink particles from the subarachnoid spaces into the Virchow-Robin perivascular spaces, do not necessarily disprove the generally accepted view of a movement of the lymph, in the perivascular spaces, in the opposite direction, i.e. towards the subarachnoid spaces.

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PERCEPTUAL PATTERNS DURING RECOVERY FROM GENERAL ANAESTHESIA*

BY

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In a series of previous communications the examination of cutaneous sensation by the method of double simultaneous stimulation has been described (Bender and Furlow, 1944 and 1945; Bender, 1945; Bender and Teuber, 1946; Bender, 1948). When double rather than single stimulation is employed, the phenomena of extinction, obscuration, and displacement make their appearance. In these phenomena one of the two simultaneously applied stimuli is either not perceived at all (extinction), perceived as diminished in intensity (obscuration), or perceived as localized to a part of the body other than that stimulated (displacement) (Bender, 1951). Furthermore, these phenomena do not occur in a haphazard fashion. A repeatedly observed and predictable pattern of perception has been described in cutaneous testing by double simultaneous stimulation. Thus it is possible to predict which of the two stimuli will be accurately perceived, and which will be extinguished, obscured, or displaced. The accurately perceived stimulus has been termed the dominant one. After numerous studies of different parts of the body with double simultaneous stimulation, a pattern of dominance has been described. The face is most dominant, the hand is least dominant, and other body areas lie in a predictable order of dominance between the face and hand (Bender, Shapiro, and Schappel, 1949).

These phenomena and patterns of dominance were first described in patients with disease of the brain and spinal cord. They were later found to be a prominent feature of the response of normal children to double simultaneous stimulation (Bender, Fink, and Green, 1950). The normal adult may make errors on the first few trials of double simultaneous stimulation, provided the subject is not previously acquainted with the test and is given no preliminary instructions other than the command to close the eyes. In the errors made by normal adults on these initial trials of the " face-hand test " (simultaneous stimulation of face and hand with eyes closed) the pattern of face dominance has been clearly shown (Fink, Green, and Bender, in press). Following these initial errors the normal adult successfully perceives and localizes two simultaneous stimuli and gives consistently correct responses on all subsequent trials. From this point on, in the absence of extinction and displacement phenomena, the patterns of dominance can no longer be investigated in the same subject.

The present study demonstrates that these patterns exist in the normal nervous system, but are inconspicuous unless certain reversible conditions of testing are introduced: in this case the clouding of the sensorium produced by a general anaesthetic. The method was suggested by the following observations.

We observed that the highest incidence of extinction and displacement phenomena in adults is found in patients with an organic mental syndrome, in whom there is an alteration in the state of consciousness; and that when these phenomena are observed in patients with organic disease of the brain, their severity and extent are increased by the intravenous administration of sodium amytal. It was also found that extinction and displacement occurred in patients without organic disease, but in whom mental confusion developed following electric shock therapy. This was especially true when a barbiturate had been administered preceding the convulsive therapy. With this in mind, a more profound pharmacological change in mental function, such as that produced by anaesthesia, was investigated. It is the purpose of this study to demonstrate these patterns of perception in the normal adult in whom a temporary reversible organic mental syndrome is produced by general anaesthesia.

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Material and Methods

The subjects were 34 patients chosen at random from the general surgical wards of Bellevue Hospital. No patients with disease of the brain or with mental changes were used in this series. With few exceptions, they had had common abdominal or gynaecological surgical procedures. All had had general anaesthesia for a minimum of one hour, many for two or three hours, or more. Three-fourths of the patients received cyclopropane, while the remainder received various combinations of intravenous barbiturates, nitrous oxide, and ether. The patients ranged in age from 13 to 73 years.

Initial examinations were performed at odd intervals during recovery from unconsciousness, varying from 30 minutes to seven hours following cessation of anaesthesia. Therefore, a large variety of mental syndromes were encountered. Most of the patients were sleeping, and had to be awakened for the examination. They were then told that a test to check the degree of recovery from anaesthesia was to be performed.

The cases tested in the early stages of recovery from anaesthesia showed a severe organic mental syndrome, with disorientation for time and place, loss of memory for the operation, rambling, confusion, disconnected speech, and inappropriate answers to questions. Some of the patients misidentified the examiner, others showed uninhibited behaviour, such as disrobing, striking or spitting at the examiner, and spontaneous discussion of intimate sexual material as in sodium amytal interviews. Some of the patients showed right-left disorientation when asked to hold up the right or left hand, but all could point to a single spot on their body that had been touched by the examiner.

Those patients with severe organic mental syndrome due to anaesthesia had an extremely short span of attention, often falling asleep in the middle of a sentence. The majority of patients, however, were sufficiently recovered so as to be oriented for time and place, and, although drowsy and mildly annoyed at the examination, were extremely cooperative throughout the testing. They tended to remember the examination on subsequent days, while the group with severe organic mental syndrome often had no memory of the test or the examiner 24 hours later.

The patient was urged to stay awake, to pay attention, and to try to cooperate. He was then told to close his eyes and was touched briefly but firmly with the examiner's two forefingers on one cheek (face), and the contralateral hand (any part of the hand or fingers). Care was taken to apply the stimuli simultaneously, and with approximately equal pressure and duration. Immediately following this, the patient was asked to report what he had perceived, and then to indicate the location of the percept reported, if he had not already done so. In several of the most clouded cases, this procedure was insufficient to orient them to the test situation. They were then told that they would be touched on the skin and were to indicate where they felt the sensation. If the patient did not at any time report two stimuli, he was specifically questioned, toward the end of the test series, as to whether any other stimuli other than those reported were felt. This was usually unnecessary as most patients reported two simultaneous percepts at some time during the test. If the patient became drowsy and lost contact, he was repeatedly roused and the test instructions repeated.

In patients whose verbal reporting was confused by rambling, disconnected speech and extraneous associations, a localization could often be obtained by asking the patient to point to the spot stimulated.

The recording of responses was not begun in the more clouded cases until the patient was sufficiently cooperative and oriented to the examination to give a minimum of 20 consecutive responses. When defects in sensation were noted on the day of anaesthesia, the examination was repeated on subsequent days until responses showed the normal adult pattern, i.e., correct localization of two simultaneous stimuli.

The first few stimulus combinations were made to the face and hand as follows: (1) face and contralateral hand, (2) opposite side of the face and contralateral hand. Then the homolateral face and hand were stimulated on each side. Following this, other parts of the body were stimulated, such as face-face, hand-hand, shoulder-hand, etc., always returning to the face-hand combination.

When the extinction phenomenon is observed the part of the body where the stimulus is felt has been defined as dominant to the part where the applied stimulus is not perceived.

Results

All of our patients showed these effects on the initial trial, which will be considered separately from subsequent multiple trials.

Response on Initial Trial.—On the initial trial, which was always the " face-hand test " (one cheek and contralateral hand), 33 of the 34 patients reported the face stimulus, but not the stimulus applied to the hand. The single exception was an unusually alert patient who had recovered to the extent that she had no obvious mental changes. She reported the face stimulus and stated that she was " not quite sure if there was another one on the hand ". She demonstrated obscuration of the hand stimulus as opposed to the extinction of the hand stimulus seen in the other 33 cases.

Thus, in this group of 34 patients in varying stages of recovery from general anaesthesia the incidence of face dominance was 100% on the initial trial of the " face-hand test ".

Response on Subsequent Trials.—The examination was continued for 20 to 50 trials per test period, or until responses were consistently normal. There were eight patients who gave a correct response to the " face-hand test " within the first four trials, and consistently correct responses thereafter, i.e., a normal adult response to the test. They tended to be the most cooperative, alert, and best oriented of the subjects. This correct response to the test

within four trials has been shown in a previous study to occur in 90% of normal adults (Bender and others, 1950).

There was another group consisting of seven patients who gave extinction or displacement responses for a greater number of trials, followed by occasionally correct responses, and finally consistently correct responses. This occurred within five or 10 minutes, i.e. within the first test period. It has been emphasized that the normal adult may make errors on the first few trials of the " face-hand test ", but suddenly becomes aware of the aspect of " two-ness " of the test. From this moment in the examination, marked by the first awareness of the existence of the second stimulus, the normal adult is consistently accurate in his report of the two stimuli. Thus, these seven patients constitute a borderline, but nevertheless abnormal group inasmuch as their awareness of the double stimuli was still followed by extinctions or displacements, in contrast to the normal.

The remaining 19 subjects continued to show extinction and displacement responses throughout the first test period, 20 to 50 consecutive trials over a period ranging up to 20 minutes. These 19 subjects showed the severest mental changes following anaesthesia, and it was in this group that the defect in perception sometimes persisted for more than 24 hours.

The time of the first test period ranged from one to seven hours after the patient was returned from the operating room. In general, the severity of the perceptual defect depended upon the length of time elapsed between cessation of anaesthesia and the first examination. The longer the interval, the less the probability of abnormal responses. This was a general trend. However, there was considerable overlapping in speed of recovery from patient to patient, probably due to a host of factors, such as depth of anaesthesia, age of patient, variation in preoperative medication, narcotics given postoperatively, amount of pain being experienced during testing procedure, personality and cooperativeness of patient, etc. A tendency for the older patients to recover more slowly was observed.

In six patients whose course of recovery was slow, the test periods fell in comparable time intervals, so that the decrease in errors on the " face-hand test " may be depicted graphically. In these six cases the first test period fell within one to three hours following anaesthesia, the second from three to seven hours, and the third from 27 to 32 hours respectively. The averaged errors on the first four trials of the " face-hand test " in each test period have been plotted against the time following anaesthesia. All six patients eventually made no errors when recovery was complete. However, the anaesthetic prolonged the " learning " of the response from the few seconds required by the normal adult to many hours as shown on the graph (Fig. 1).

Phenomena of Extinction and Displacement.—The errors fell into two categories. In the first, only one of the two stimuli was felt (dominance of one and extinction of the other), and in the second both stimuli were felt, one correctly localized, but the other mislocalized (dominance of one and displacement of the other). Thirty-three of the 34 patients showed the extinction phenomenon, although in the eight who gave normal records, extinction was only observed within the first four trials of the face and hand.

Twenty patients showed ipsilateral displacement, such as from the hand to the face on the same side. Eight patients showed allesthesia (displacement of stimuli across midline to the opposite side of the body). However, the occurrence of allesthesia was rare even in patients giving this response. Ipsilateral displacement was much more common than allesthesia, and was often seen persistently throughout the testing period. Extinction was most common.

Patterns of Dominance.—When extinction was observed, the face was seen to be dominant to the shoulder, hand, and foot. The shoulder was dominant to the hand and the foot was dominant to the hand. These patterns confirm results of previous studies. This last pattern of dominance (foot over hand) was especially striking in view of the fact that the bedclothes were never removed from the feet of these post-operative patients, the stimuli being administered to the blanket-covered toes and to the skin of the hand. Extinction of the hand stimulus still occurred more frequently.

There were occasional exceptions to all these patterns, but statistically the percentage of response which fell into the patterns far outweighed the exceptions. The pattern of face dominance over the hand seemed to be most conspicuous. Defects in the face-hand test could often be elicited long after double simultaneous stimuli could be correctly localized on other parts of the body. In this connexion it must be reiterated that the face is highest and hand is lowest in the order of dominance.

When displacement occurred the error was usually in the direction of the dominant stimulus. Again it was most frequent in the face-hand combination. The most commonly observed displacement response was on stimulation of one side of the face and the contralateral hand, in which case the patient reported percepts on both sides of the face.

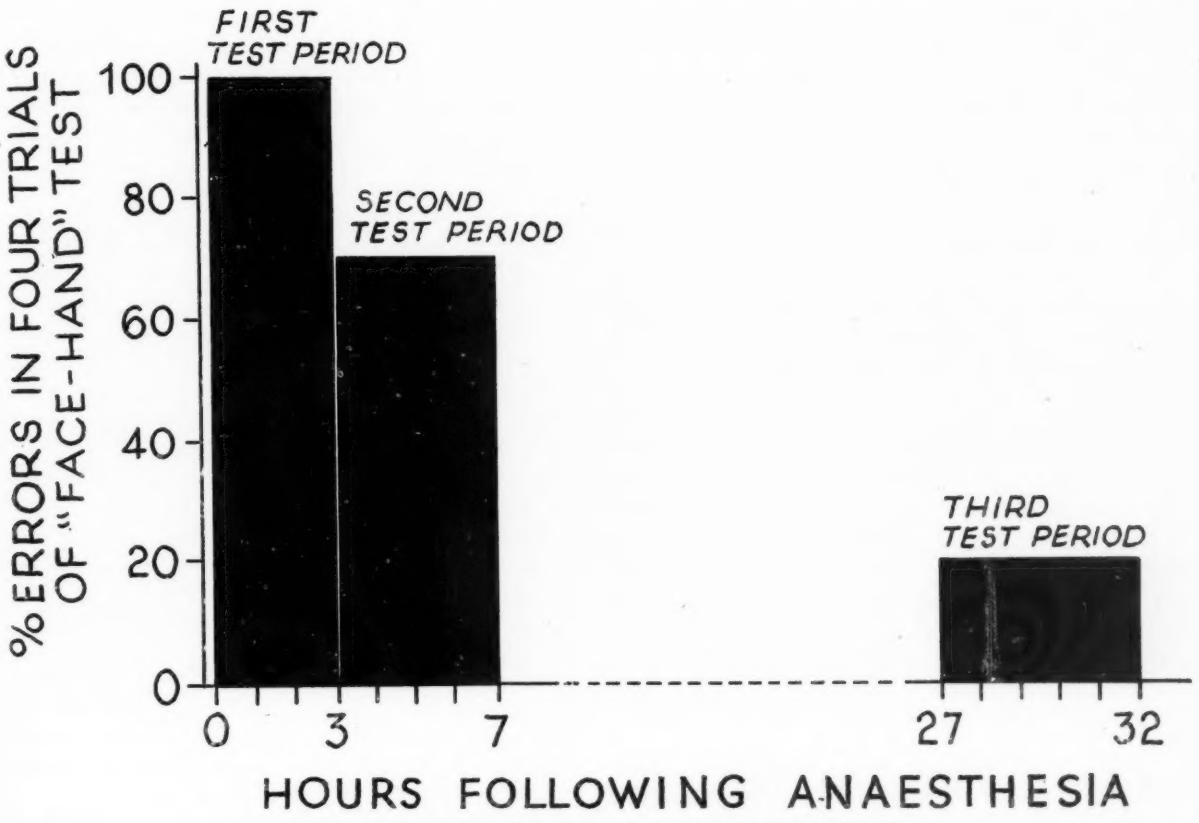

FIG. 1.—Averaged results for six patients after four initial trials of the "face-hand test" in consecutive test periods.

Discussion

During recovery from anaesthesia, patients have been examined by the method of double simultaneous stimulation of cutaneous modalities. Many errors are made in perception and localization of the stimuli, but it has been found that the errors are consistent and show a pattern in all cases tested. One can predict which of the two stimuli will be accurately perceived (defined as the dominant stimulus), and which will be mislocalized (displacement), or not perceived at all (extinction). Thus a pattern of dominance can be found for any two non-homologous areas of the body, and is seen most clearly when the face and hand are the areas tested. We have observed that following a prolonged period of unconsciousness, produced by a variety of anaesthetic agents in the normal nervous system, these patterns were clearly demonstrable. They occasionally persisted for a period of days. Thus, on the initial trial of the "face-hand test", up to seven hours following general anaesthesia, all 34 of our patients showed face dominance. In a previous article the incidence of face dominance on initial trial of the face-hand test has been found to vary among the different populations tested (Fink and others, in press). Results are shown in Table I.

TABLE I

Group Tested	Incidence of Face Dominance on Initial Trial of "Face-Hand Test" (%)
Normal subjects (above age 12 years)	48
Normal children (age 7 to 12 years)	47
Normal children (age 3 to 6 years)	82
Organic mental syndrome	90

It is apparent that during recovery from anaesthesia the defect in sensation, as judged by this test, is comparable in degree to that in severe disease of the brain and in very young children.

Following the initial test, eight of our patients revealed the normal pattern of response, i.e. within approximately four trials of the "face-hand test"; they localized the two stimuli correctly, and made no further errors. However, the remaining 26 patients showed a response pattern comparable to that seen in young children and in patients with

organic psychosis. The three groups are similar with respect to the patterns of dominance and the persistence of extinction or displacement responses beyond the first few trials of double simultaneous stimulation. The difference in these three groups is that the errors in patients with mental changes due to anaesthesia last only a few minutes to hours, depending upon the severity of the anaesthesia and post-anaesthetic period.

It should be emphasized again that once a normal adult " gets the idea of two-ness " in the test, as evidenced by a correct response to double stimulation, he is remarkably accurate on all subsequent tests, even with days intervening. Yet patients with an organic mental syndrome, normal children, and the 26 of our cases showing abnormal records, still gave extinction or displacement responses following one or more correct responses to double simultaneous stimulation. That these 26 abnormal records resulted from the anaesthesia and not from disease of the nervous system is proved by the return of all patients to normal adult responses some days following the anaesthetic. Patients with organic brain disease make persistent errors on subsequent days, no matter how long the testing is continued.

Many of the patients used in this study were drowsy and therefore inattentive. We know that attention is a variable affecting our results, as well as factors of type and intensity of stimulus, timing, area tested, etc. But the assertion that inattention is an explanation of these phenomena is clearly negated by the patterns of the errors observed (Critchley, 1949). If inattention were the entire explanation, we would expect the errors to be random, so that defects would occur in face as well as in hand perception. On the contrary, they were predictably patterned, and the patterns were comparable, regardless of the degree of attention of the patient. Occasionally, more severe, yet still predictable and consistent defects, were noted in patients sitting up in bed and anxious to cooperate, than in drowsy patients who fell asleep between stimuli and begged the examiner to " let me alone ".

The significance of this study lies in the demonstration of extinction, displacement, and patterns of dominance when neural function is altered pharmacologically in adult subjects with normal nervous systems. The data reported here may be correlated with three sets of previous observations, namely the demonstration of similar phenomena in normal children with decreasing incidence as older age groups are tested ; the high incidence of similar phenomena in patients with organic mental syndrome, in whom there is clouding of the sensorium (Fink and others, in press) ; and the pattern of face dominance seen in normal adults on the initial trials of the " face-hand test ", but the absence of face dominance on subsequent trials.

In the light of the foregoing, one might speculate that the capacity to perceive and localize two simultaneous stimuli is related to maturation of the nervous system, and that before this capacity is fully devleoped the patterns of dominance are clearly in evidence, as seen in children. Our results show that these patterns of childhood sensory organization are a latent potentiality of the normal adult nervous system. The variety of drugs found to be capable of eliciting these patterns are all in the class of general anaesthetics. All are known to act upon the central nervous system in such a way that the " higher psychic functions " and state of consciousness are predominantly affected.

Henry Head stated that " should the disturbing agent exert a universal effect, as is the case with chloroform, one function after another disappears in order, beginning with those of highest rank and culminating with the most mechanical and pre-ordained response " (Head, 1923). He also noted that regression and recovery of function traverse the same steps, but in opposite directions (Head, 1926). Thus, the organic mental syndrome is one of the earliest effects of the administration of a general anaesthetic and one of the last effects to disappear during recovery. Correlated with this alteration of consciousness is the appearance of normally inconspicuous patterns of perceptual organization. In a sense the maturation of perceptual function has been transiently reversed, a so-called " regression ". Pharmacological interference with the most highly integrated levels of function leaves the more basic patterns of organization functionally isolated. This is in keeping with Jackson's (1887) concept of levels of integration in which the breakdown of " higher " integrative functions results in a release of " lower " types of organization.

Summary

When two simultaneous stimuli are applied to widely separated cutaneous areas one of the stimuli may not be perceived (phenomenon of extinction), or may be perceived but mislocalized (phenomenon of displacement).

Phenomena of extinction and displacement have been elicited in subjects who show no disease of the nervous system, as temporary findings during the course of recovery from various general anaesthetics.

Patterns of sensation described in previous studies of patients with organic mental syndrome,

of normal children, and of normal adults have been confirmed.

The existence of these patterns has been demonstrated in a transient, pharmacologically induced alteration of neural function.

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CESSATION OF DREAMING AFTER BRAIN INJURY

BY

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Loss of visual imagery in dreams was first described by Charcot (1883) in an early case report of visual agnosia. The patient, a linguist and classical scholar of some eminence, sustained a sudden and virtually complete abolition of visual memory following a cerebral vascular catastrophe. Although formerly an excellent visualizer, the patient was quite unable to imagine the appearance of his wife and children, or to summon up a mental image of his childhood home. This defect extended to all spheres of visual memory, remote no less than recent, and affected the visualization of colour as markedly as that of form. It is also said to have deprived the patient of visual experience in his dreams. In view of the patient's well-preserved intelligence and general memory, the defect was regarded by Charcot as a circumscribed visual amnesia, and held by him as wholly responsible for the agnosic state.

Although it is not now customary to attribute visual agnosia, wholly at least, to defects of visual imagery, it is a matter for regret that so few investigators have studied the fate of dream imagery in agnosic syndromes. Russell Brain (1941), it is true, comments that one of his patients, a boy of 15 with persistent agnosia and kindred defects, continued to experience visual imagery in his dreams. On the other hand, the patient reported by Adler (1944, 1950) is said to have ceased to experience visual imagery in dreams after the injury which gave rise to a severe agnosic syndrome. In this case, however, unlike Russell Brain's, visual imagery in the waking state appears to have been much depressed. More recently Russell Brain (1950) has referred to a patient who presented a circumscribed loss of visual imagery in the absence of visual agnosia. In this case, too, visual dreaming ceased entirely though the patient continued to experience non-visual dreams. It is therefore probable that loss of visual imagery in dreams is associated with loss of visualization rather than with loss of visual recognition. The whole problem of the relation between visual agnosia, loss of visual imagery, and changes in dream activity is obviously in need of further elucidation.

In the course of an investigation of psychological changes associated with posterior parietal lesions, three patients have been encountered in which *cessation of dreaming* was spontaneously reported as an after-effect of brain injury. This loss appeared to be permanent in two cases, and temporary in one. All patients reported marked defects of visualization in the waking state together with some degree of visual-spatial loss. The patients were of good previous intelligence level, and two had received a university education. Although studies of imagery are inevitably lacking in objective control, there was no obvious reason to question the reliability and good faith of the patients' testimony. Despite the small number of cases so far studied, it is felt that the whole question of dream activity in its neurological aspects is of sufficient interest to justify a brief communication.

Case Reports

Case 1 (No. 9693).—An officer, aged 26, right-handed, sustained a wound of the right posterior parietal region of the brain in August, 1944 (Fig. 1). The fragment of metal seen in Fig. 1 was removed at operation two days after wounding. His principal disabilities at first were complete left homonymous hemianopia, left hemianaesthesia and mild pyramidal tract signs. One month later, neurological findings (apart from hemianopia) were minimal, but fairly marked topographical loss and defects of visual recognition were in evidence. Some defects of visualization and spatial judgment were shown in psychometric tests. On re-examination six years after injury, the hemianopia was still present and the patient reported moderate residual topographical impairment and some disturbance of visual memory. He stated that he had formerly been a good visualizer, but at present his visual images are " very dim " and hard to evoke. He then spontaneously remarked that he seemed to have " lost the habit " of dreaming, and that he had " almost no dreams nowadays ". In general, the patient's account of his disabilities led us to conclude that all thought processes of a predominantly visual character (including dreaming) were markedly depressed.

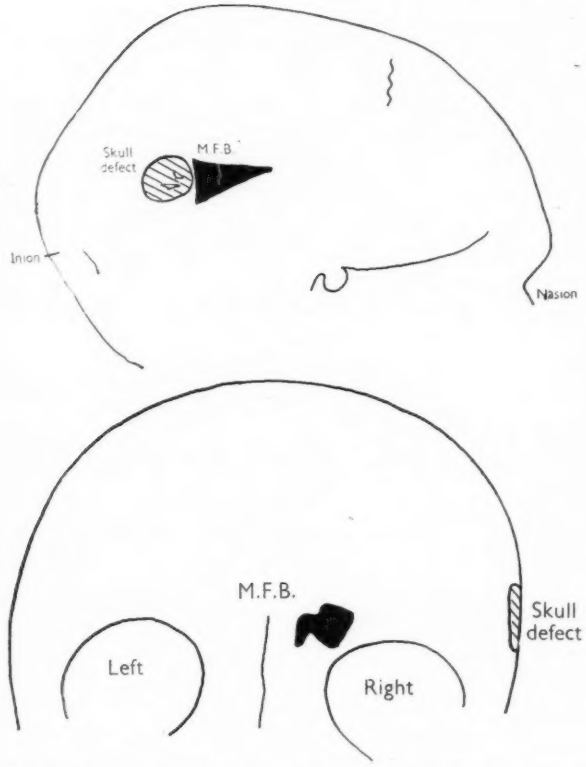

FIG. 1.—Tracing of skull radiographs of Case 1 to show position of skull defect and metal fragment.

There was no suggestion of a general memory loss for recent events which might have provoked amnesia for dream experiences.

Case 2 (No. 9963).—A corporal, aged 21, right-handed, sustained a parasagittal posterior parietal mortar wound in September, 1944, which involved the parieto-occipital areas of both sides, predominantly the left (Fig. 2). There was retrograde amnesia for several hours, and the duration of post-traumatic amnesia was about a week. Principal neurological disabilities after remission of the post-traumatic confusional state were bilateral visual field defect (complete left homonymous hemianopia and visual disorientation in right half fields), impairment of joint sense in the right limbs, and dysphasia. There was also mild dyspraxia and topographical loss. On re-examination six years after injury, the patient presented a left homonymous hemianopia and mild residual dysphasic and dyspraxic signs. There was also some topographical and related visual memory loss. He reported that his visualization was still very defective. Before the injury, he had regarded his capacity for visualization as moderately good. Now, however: " . . . . if someone says : ' Can you visualize what your home is like ?' ' Well, I can do that, but I can't visualize a lot of things, such as faces sometimes or places I've been to and tried to recall '." He then added spontaneously : " And I never dream ". On further inquiry, he replied that he used to dream " fairly often " before his injury, but that he *had not had a single dream in the last six years*. It also transpired that he now experienced no hypnagogic imagery preceding the onset of sleep. " Lying awake at night trying to go to sleep, I think only in words, never in pictures." As in Case 1, it appeared unlikely that the apparent loss of dreaming could be explained on the basis of a recent memory defect.

Case 3 (No. 8846).—An officer, aged 32, left-handed, sustained a mortar wound of the right posterior parietal area in June, 1944 (Fig. 3). The retrograde amnesia was a few seconds ; the post-traumatic amnesia was about one hour. One week after injury, the principal neurological findings were : left homonymous lower quadrantic hemianopia, severe left hemiplegia and cortical sensory loss, and moderate dysphasia. One month after injury, speech and motor function showed considerable improvement, but there was evidence of topographical loss, dressing dyspraxia, confusion of right and left and visual-constructive disability. Psychometric testing at this stage showed some intellectual retardation and marked impairment on all tests commonly held to demand visualization (e.g. " cube-counting "). On discharge, six months after injury, residual disabilities were slight motor weakness of left arm and leg, mild left-sided sensory signs, slowness of speech and reading, and some topographical loss. The visual fields were normal. Despite these handicaps, the patient was able to return to an active and responsible position in civilian life.

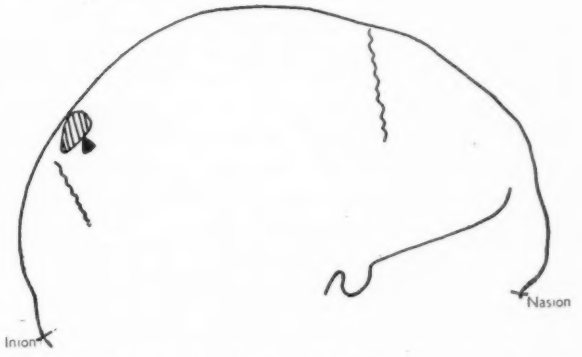

FIG. 2.—Tracing of skull radiograph of Case 2 to show site of wound.

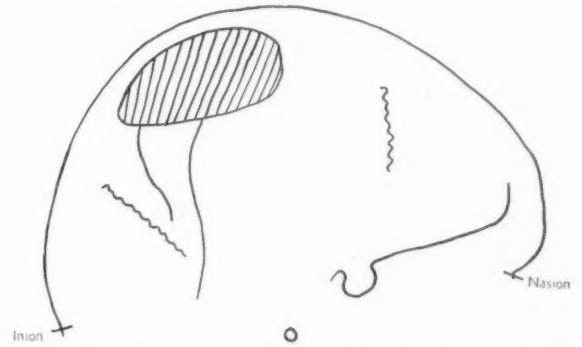

FIG. 3.—Tracing of skull radiograph of Case 3 to show skull defect after operation.

In a progress report five years after discharge, the patient stated :

" An interesting factor is that I have been dreaming again—a thing which I have not done since my injury in 1944."

When interviewed one year later, he confirmed this statement, and added that he now thought that he dreamed as frequently as before his injury. His dreams, moreover, were predominantly visual. He also thought that waking visualization had greatly improved during the last year or so. In this case, then, we may note the restitution of dreaming five years after an injury which caused pronounced defects in higher visual functions.

Comment

The above three cases are of interest in presenting marked disturbances of visualization and visual memory as after-effects of brain injury. Case 1 claimed to have been a strong visualizer before his injury, and reported that his visual images had become dim and difficult to evoke. Case 2 reported similar difficulties, and stated that he no longer experienced visual phantasy in the hypnagogic state preceding sleep. Case 3 reported that during the five years in which he experienced no dreams, his capacity for waking visual imagination and recall was much depressed. In general, it may be safely concluded that visual thinking was affected in all three cases. If we regard dreaming as a predominantly visual thought-process, it is not altogether surprising to note its loss in these patients. Case 1 stated that he had " lost the habit " of dreaming almost completely. Case 2 claimed that he had completely ceased to dream since his injury. Case 3 spontaneously reported re-appearance of dreaming after five years of allegedly dreamless sleep. On present evidence, then, it would appear that dreaming is much depressed in patients with impaired visualization due to injury to the occipito-parietal region of the brain.*

It cannot yet be stated with confidence whether cessation of dreaming occurs only in association with occipito-parietal lesions, or whether it is also found with lesions involving other areas of the cortex. In preliminary inquiries, we have been unable to establish consistent changes in the frequency or character of dreaming in several patients with lesions of the frontal lobes. On the other hand, reduction of dreaming has been reported in a number of patients following *pre-frontal leucotomy* (Partridge, 1950 ; Slater, personal communication, 1951). Partridge comments that " a large number of patients observed that post-operatively they slept—as one of them phrased it—' dead ', and several remarked that their sleep had become unusually dreamless. This latter tendency, however, disappeared, as did the undue heaviness of sleep, between six months and a year after operation, if not before ". Whereas it is evident that Partridge is disposed to attribute post-operative reduction in dreaming to increased depth of sleep, one may point out that it could equally well be due to amnesia on awakening, or to some more generalized depression of cerebral function. In view of the locus of the surgical lesion, however, it is *prima facie* unlikely that the change is due to the implication of higher visual mechanisms, as has been postulated in the present cases. At the same time, the possibility that loss of dreaming in the latter depends, in part at least, on some more general depression of cerebral activity cannot be excluded. A more detailed study of dreaming in cases with cerebral involvement, both diffuse and circumscribed, will obviously be necessary before final conclusions can be drawn.

It is in order to inquire briefly whether data obtained from experiments on cortical stimulation in man are relevant to the present discussion. As is well known Penfield and Erickson (1941) have reported dreamlike states following stimulation of points on the temporal lobe in cases of " psychical " epilepsy. In one of their cases, the subjective phenomena experienced in attacks, and reduplicated by stimulation, had actually formed part of a recurrent nightmare. In a discussion of these findings, Penfield and Erickson observe that " in dreams under normal circumstances there may be a sort of patterned neuronal activity within the temporal cortex of one or both sides. One may be said to dream with his temporal lobes ".

In a more recent contribution Penfield and Rasmussen (1950) lay stress on the undeniable similarity between mental states induced by stimulation and ordinary dreams, and regard both as due to the activity of neuronal patterns located in the temporal area. Suggestive though these findings are, it must none the less be pointed out that no case is known to the present writers in which *abolition* of dreaming has been reported to follow temporal lobectomy. Further, it appears most unlikely that dream-like states could be provoked by stimulation in non-epileptic subjects or in cases such as our own, in which higher visual activity had already been depressed by a circumscribed cerebral lesion. The significance of Penfield's findings for any theory of the cerebral localization of dream processes must therefore be evaluated with caution.

In conclusion, we may enquire whether there is any parallel to be drawn between the cessation of

* It is probable that in such cases dreaming is affected much more frequently than is commonly supposed. We are indebted to Prof. R. C. Oldfield for the information that a patient with right occipito-parietal brain abscess, operated upon by Sir Hugh Cairns in 1938, has entirely ceased to dream in the 13 years which have elapsed since operation.

dreaming in cases such as those reported here and the disturbances of language observed in cases of aphasia. From the psychological point of view, there is some reason to regard dreaming as an expressive function, albeit at an inferior (hyponoic) level. As Dalbiez (1941) puts it: "Language expresses thought vocally, the dream expresses it psychically. We may say that the dream is a natural and individual psychic language". On this view it may be argued that, just as the aphasic is unable to express his thought in propositional form, so the agnosic patient may fail to express his ideation at the lower level of phantasy and dream. While not denying that the trend and content of any given dream, or indeed of any given proposition, cannot be interpreted without reference to psychological factors, we would like at the same time to suggest that visual thinking, dreaming and imagination are liable to organic dissolution in a manner directly comparable to the dissolution of symbolic thought in aphasia. But whereas aphasia is specifically associated with lesions of the dominant hemisphere, disorders of visual imagination appear liable to follow lesions on either side, and to be especially marked in cases with involvement of the occipito-parietal region. Their more complete elucidation remains a task for future inquiry.

Summary

Three cases are briefly reported in which cessation of dreaming was spontaneously described as an after-effect of occipito-parietal brain injury. The locus of the lesion was right-sided in two cases (one of which was a left-handed man) and bilateral, though predominantly left-sided, in one. This loss appeared to be permanent in two cases and temporary in one. Depression of dreaming was associated with impaired visual imagination and memory in the waking state and with residual topographical loss. All three patients were of good pre-traumatic intelligence, and reasonable confidence could be placed in their testimony.

Kindred observations from the literature of visual agnosia are mentioned. It is tentatively suggested that dreaming is likely to be affected only in those agnosic states in which there is appreciable impairment of visual imagery.

Reduction of dreaming as an early sequel of prefrontal leucotomy and the dreamlike states which may be induced in certain cases of epilepsy by temporal lobe stimulation are briefly discussed.

It is tentatively suggested that depression of dreaming and visual imagery in consequence of brain injury may be regarded as a dissolution in some respects analogous to aphasia.

We wish to thank Dr. W. Ritchie Russell for his generous encouragement and kind permission to quote extracts from case records at the Oxford Head Injuries Bureau and to interview patients admitted under his care. We have also to express our gratitude to Dr. W. Russell Brain for his helpful comments on this paper.

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AN INVESTIGATION OF THE PSYCHIATRIC ASPECTS OF DISSEMINATED SCLEROSIS

BY

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Many investigations have been made of the psychiatric aspects of disseminated sclerosis, but there is little agreement on the findings or on their significance. In this paper a report is made of an investigation of 100 patients suffering from disseminated sclerosis and of 100 control patients, with regard to premorbid personality, emotional antecedents of the illness, and psychiatric emotional and intellectual changes following the illness.

Previous Investigations

Premorbid Personality.—A characteristic premorbid personality of hysterical type has been noted by some authors (Langworthy, 1950; Grinker, Ham, and Robbins, 1950). The majority of authors, however, do not consider the premorbid personality of importance. Charcot (1877) remarked of his male patients :

> " These are, for the most part, persons who have lost caste, and who, thrown out of the general current, and too impressionable, are ill-provided with the means of maintaining what, in Darwin's theory, is called the 'struggle for life' ", but Charcot concluded " in the pathological antecedents of the patients themselves we generally find nothing but vague indicia."

Neither Brain (1930) nor Wilson (1940) mentioned any characteristic premorbid personality.

Emotional Antecedents.—The earliest clinical account of disseminated sclerosis associated the onset of the disease with emotional stress. Augustus d'Este (Firth, 1948) wrote in his diary :

> " I attended his funeral : there being many persons present I struggled violently not to weep. I was however unable to prevent myself from so doing. Shortly after the funeral . . . . my eyes were so attacked that when fixed upon minute objects indistinctness of vision was the consequence."

Charcot (1877) stated :

> " The circumstances most commonly assigned as causes of this disease, by patients, appertain to the moral order—long-continued grief or vexation . . . the aetiology is a somewhat trite one, such as may be met with again, as it were, at the beginning of all the chronic diseases of the nervous system."

Moxon (1875) gave a dramatic instance of the association of the onset of the disease with an emotional shock :

> " She ascribed the commencement of her ailment . . . to a shock received on the occasion of her sister's death in a confinement, by seeing the doctor come with hands covered with blood into the room, and being told her sister was dead . . . At the time of the shock, she had at once a hysterical fit, and after this had weakness of the legs, which disappeared soon, but returned in six months."

There have been many other striking examples recorded of emotional stress antedating manifestations of the disease, but few adequate control observations have been recorded. Braceland and Giffin (1950), who studied 50 control patients, concluded that " the necessity and sufficiency of psychological trauma required to explain the genesis of these specific symptoms were not demonstrated in our cases ".

The influence of emotion in causing a transient exacerbation of symptoms due to an established lesion was mentioned by Brickner and Simons (1950), who referred to two patients, but there has been little emphasis on this aspect of the disease.

Changes in Personality.—There is a divergence of opinion on changes during the course of the disease.

Psychiatric Changes.—Brown and Davis (1922) stated : " Apart from certain mood changes, for example euphoria, multiple sclerosis patients usually retain the same personality that they had before their illness began ". Braceland and Giffin (1950) found changes dependent on the stage of the disease : in the early stage " the patient's reaction in the largest measure is determined by his mode of response to incapacity or dysfunction induced by any type of disease ", whereas in the chronic stage " the individual now reacts with the classical signs of

organic disease of the brain ". Hysterical symptoms have classically been associated with disseminated sclerosis. Wilson (1940), however, wrote : " At early periods fugitive symptoms may well give rise to a suspicion of hysteria, but genuine hysterical phenomena are distinctly rare, and their development a mere coincidence ".

Estimates vary of the incidence of psychosis in disseminated sclerosis ; psychotic manifestations in the disease are of no characteristic pattern (Ombredane, 1929; Langworthy, Kolb, and Androp, 1941).

Emotional Changes.—Most authors record as evidence of euphoria a statement by the patient that his mood is consistently cheerful. Others, without apparent inquiry of the patient, deduce his mood from his external appearance. The danger of this procedure is well shown in an extract from the diary of Barbellion (1948), a sufferer from the disease :

> " I am astonished at the false impression these entries give of myself. The picture is incomplete anyhow. It represents the cloud of forebodings over my inner self, but does not show the outward front I present to others. This is one of almost constant gaiety—unforced and quite natural."

Other authors record a " relative euphoria," a contrast of this outward front with what they consider should be the patient's appropriate affective reaction ; they thus introduce a further distortion into a record of mood changes. It is, therefore, not surprising that the diverse connotations given to the term euphoria have led to varying estimates of its frequency (Langworthy and others, 1941 ; Borberg and Zahle, 1946 ; Mackay, 1950 ; Brickner, 1950 ; Grinker, Ham, and Robbins, 1950). Braceland and Giffin (1950) examined 75 patients, and found euphoria in 10%, depression in 20%, lability of mood in 18%, and an unusual degree of irritability in 12%. They also found that " all patients who exhibited euphoria as their predominant mood gave evidence of widespread cerebral disease or disturbance ". Their conclusions are of particular interest in that many of their cases were from the series of Cottrell and Wilson (1926), who found that 63 of 100 consecutive patients stated that their mood was consistently cheerful or happy, while in 10 it was consistently sad or unhappy.

Increase in lability of affect and decrease in control of the expression of emotion have both been noted, although at times the context does not allow of their differentiation. Charcot (1877) stated that " it is not rare to see these give way to foolish laughter for no cause, and sometimes, on the contrary, melt into tears without reason ". Moxon (1875) stated : " . . . one hears bursts of unmeaning laughter, and in conversation the patient will laugh incontinently where no sound-minded person can find cause for merriment. Weeping is equally out of just relation to its proper cause ". Cottrell and Wilson (1926) found that 95 of 100 cases showed " facility and amplification of emotional expression (affect) ", (71 of these showing constant smiling or laughing), and that in 96 there had been a change in this respect since the illness began. The symptom was not always as evident to the patient as it was to the examiner, since only 87 reported an awareness of change in emotional expression. These authors also emphasized the finding that 84 patients admitted to " eutonia ", a sense of physical well-being in striking contrast to their crippled physical state. They considered that change in mood, change in bodily feeling, and change in emotional expression and control constituted a diagnostic triad of greater value than any neurological symptom-complex, and postulated that it was due to dysfunction of the thalamus.

Intellectual Changes.—Clinical estimates of intellectual deterioration resulting from the disease have varied widely. Charcot (1877) stated : " there is marked enfeeblement of the memory : conceptions are formed slowly : the intellectual and emotional faculties are blunted in their totality ". Moxon (1875) found enfeeblement of mind less frequently : " This is not forced upon the observer at all obviously in many cases ; in others it is among the early and evident symptoms ". Ombredane (1929) found intellectual deterioration in 36 of 50 cases : in six the deterioration amounted to dementia. In contrast, Cottrell and Wilson (1926) stated : " After careful observation we were able to demonstrate in only two cases (out of 100), any signs of actual intellectual deterioration ".

Standardized intelligence tests have recently been used in an investigation by Canter (1951) of intellectual deterioration in disseminated sclerosis. The 47 patients in his series were a representative sample of the total population of World War II American veterans in the early stages of the disease (duration one to eight years, average four years). A direct estimate of intellectual deterioration was made in 23 patients whose scores on the Army General Classification test at entry into the armed forces were available and were compared with the scores at the time of the investigation. The mean loss over an average period of four years was highly significant, and indicated that intellectual deterioration had occurred in this group. A direct estimate of intellectual deterioration, over a shorter

period of time, was made on 47 patients who were tested twice at an interval of six months with the Wechsler-Bellevue battery. When compared with healthy controls, this group showed a highly significant deterioration, even over this comparatively short time. Indirect estimates of intellectual deterioration depend on the finding that, when deterioration is present, vocabulary is maintained relatively intact, whereas performance on a variety of other tests is more severely impaired. Canter used four tests of this type : the Wechsler-Bellevue battery, the short form of the Babcock scale, the Shipley Hartford test, and the short form of the Hunt Minnesota test. Each of these tests revealed the presence of some intellectual deterioration in the group of 47 patients. Intellectual deterioration, as measured both by direct and indirect methods, increased with the neurological rating of degree of disability.

Present Investigation

Material and Method of Inquiry.—The patients with disseminated sclerosis (D.S.) were chosen at random from available patients with the disease attending the Department for Nervous Diseases, Middlesex Hospital ; these patients were however selected, in that inpatients, and to a greater extent outpatients, were as a rule not in the most advanced stage of the disease (Table I). This selection of the material would not give rise to inaccuracy in assessing the premorbid personality and the emotional antecedents of the disease, and might well render such assessment more accurate. However, changes in personality following the illness would tend to be less marked in such a series than in a series of patients with all stages of the disease evenly represented. Almost every patient knew the name and nature of his illness, and had had opportunity of meeting other patients with moderate or severe disability resulting from the disease.

TABLE I
DEGREE OF DISABILITY

		Severe	Moderate	Mild
Male :	D.S. ..	9	24	17
	Control ..	5	15	30
Female :	D.S. ..	9	15	26
	Control ..	5	22	23

Control patients were matched for sex and approximately for age at interview (Table II). All were patients of the Department for Nervous Diseases, Middlesex Hospital, and all save three were suffering from organic disease of the nervous system. The interview was accepted by the patient as an attempt to contribute further to the knowledge and management of his illness. It was considered that indifferent controls, for example patients admitted for repair of hernia, would be unlikely to be fully cooperative in an interview concerned largely with their personal life history. No patient was chosen as a control if the final primary diagnosis were one of psychoneurosis or of any disease widely considered at present to be psychosomatic in nature.

The interview took the form of a psychiatric inquiry into the patient's life history ; it was not rigidly standardized. The history of the patient's illness was taken separately, and was then correlated with the life history. Direct inquiry was later made into emotional stress antedating the onset and relapses of the disease, and into emotional and intellectual changes following on the disease. An intelligence test was performed by each patient.

Premorbid Personality.—There is no satisfying scheme of personality assessment. Nevertheless an attempt was made to assess the premorbid personality of each patient both as a whole and in more limited aspects. The assessment of personality as a whole was made in this series by allotting each patient to the appropriate class in the personality schemes of Jung (extraversion-introversion), and of Sheldon (viscerotonia, somatotonia, cerebrotonia). Jung (1928) described the introverted attitude as " hesitating, reflective, reticent ", the extraverted as characterized by " an accommodating and apparently open and ready disposition, at ease in any given situation ". Sheldon (Sheldon, Hartl, and McDermott, 1949) summarized the varieties of temperament as follows : " Viscerotonia is manifested by relaxation, conviviality, and gluttony for food, for company and for affection or social support " ; " somatotonia is manifested by bodily assertiveness and by desire for muscular activity " ; " cerebrotonia is manifested by (1) inhibition of both viscerotonic and somatotonic expression, (2) hyperattentionality or overconsciousness ". The numbers in each class did not differ significantly when patients with disseminated sclerosis were compared with the

TABLE II
AGE AT INTERVIEW AND NUMBER OF PATIENTS IN EACH AGE-GROUP

Age at Interview (years)		15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	Total
Male :	D.S. ..	—	2	6	6	11	14	6	2	1	2	50
	Controls ..	1	1	7	9	7	13	4	5	1	2	50
Female :	D.S. ..	1	3	7	11	13	5	7	2	1	—	50
	Controls ..	1	3	8	8	9	11	6	3	1	—	50

control patients. In addition the patients with disseminated sclerosis did not appear as a group to be of any other characteristic personality type or types.

Limited aspects of the personality were investigated by recording the presence or absence of the following features: (1) the occurrence of somatic symptoms (for example headache, abdominal pain) following emotional stress; (2) hysterical manifestations*; (3) obsessional traits; (4) obsessional neurosis†; (5) depressive episode; (6) marked degree of psychopathy; (7) physiological instability in childhood‡; (8) the patient's statement that he was of a worrying temperament (Table III).

TABLE III
PREMORBID PERSONALITY

	1	2	3	4	5	6	7	8
Male: D.S. ..	9	2	10	—	2	3	13	21
Controls ..	12	3	12	1	—	1	10	17
Female: D.S. ..	24	2	9	3	1	1	3	29
Controls ..	17	2	7	2	5	—	13	26

Score—see text.

to tell stories about a series of pictures presented to him; underlying tendencies which the patient will not or cannot admit are expressed in the content of the stories. Since only two patients revealed aggressive tendencies in their stories, results in the small group tested do not suggest that unexpressed aggression plays a part in the genesis of disseminated sclerosis.

Emotional Antecedents.—If emotional disturbances at a conscious level are of significance in bringing on the onset or relapse of disseminated sclerosis, such disturbances ought to be encountered more frequently before an attack of the disease in patients with disseminated sclerosis than in a control series of patients. The occurrence of an emotional disturbance at stated intervals before the onset of the disease, and the occurrence of such a disturbance for a prolonged period up to and including the time of onset, are recorded in Table IV. When the totals are compared it is found that in 38 patients with disseminated sclerosis and in 26 control patients emotional stress antedated the onset of the disease; this difference however does not quite reach the level of significance ($\chi = 1{\cdot}8$*).

TABLE IV
NUMBER OF PATIENTS (D.S.) AND CONTROLS (C.) WITH EMOTIONAL STRESS AT STATED INTERVALS BEFORE THE ONSET AND RELAPSES OF THEIR DISEASE

Sex	Group	No. of Onsets (O) or Relapses (R)	Minute	Hour	Day	Week	Month	Prolonged Strain	Total
Male ..	D.S.	O 50	—	—	1	—	3	15	19
Male ..	C.	O 50	—	—	—	—	2	8	10
Female ..	D.S.	O 50	—	—	1	1	3	14	19
Female ..	C.	O 50	—	—	—	—	3	13	16
Male ..	D.S.	R 90	—	—	—	1	3	13	17
Female ..	D.S.	R 139	—	2	3	10	8	18	41

The numbers in each category did not differ significantly when patients with disseminated sclerosis were compared with controls. The patients with disseminated sclerosis and the control patients were also compared in respect of good or bad environment in childhood, and of separation from father or from mother before the age of 15. No significant differences were found.

It has been postulated that psychosomatic disorders are due to a lack of discharge of affect through conscious channels, and in particular that unexpressed aggression may play a predominant role in this respect. Fifteen patients with disseminated sclerosis were given the Thematic Apperception Test (Murray, 1943). This test requires the subject

The tendency in patients with disseminated sclerosis for antecedent emotional stress to be reported, especially by those in whom somatic symptoms follow emotional stress, and by those of a worrying temperament, did not reach the level of significance ($\chi = 1{\cdot}0$ and $1{\cdot}6$ respectively). In the three instances of the onset of disseminated sclerosis within a week of an emotional stress, this was not of unusual degree or significance to the patient concerned, and was therefore considered unlikely to be of aetiological significance. The number of instances of emotional disturbance antedating relapses in patients with disseminated sclerosis is recorded in the same table; the figure of 25% is very similar to that obtained for the onset of the disease in control patients (26%) and suggests that emotional stress played no part in determining relapses of the disease.

* Including amnesia, blepharospasm, globus, neurasthenia, functional overlay, labour pains in a man, vomiting, and aphonia

† Including phobias, ruminations, and hypochondriasis

‡ Sleep-walking, stammering, and bed-wetting

* χ, to be significant at the 5% level, must be 2·0 or greater.

In a few instances, however, an emotional stress appears to have precipitated the onset or relapse of disseminated sclerosis. Two instances from this series, and a further six instances, selected from a larger series of 840 patients attending the Middlesex Hospital, are given below.

Case No. 80. *Relapse.*—Aged 39, one hour after receiving a letter containing bad news, she went out on her usual bicycle ride. She was only just able to return, and has not walked since that date.

Case No. 84. *Relapse.*—Aged 16 she had a severe quarrel one night with the daughter of her mother by adoption. The quarrel continued the next morning. One hour later an attack of vertigo and vomiting began.

Onset.—" N.W.J., in April, 1934, when aged 21, sustained a through and through wound of the right foot as a result of jumping on a nail. The wound was dressed, and he stayed away from work for two weeks. In July of the same year, while riding his motorcycle with his fiancée on the pillion seat, he rounded a corner at an excessive speed and had a narrow escape from a head-on collision with a car. At once his legs felt numb, ' as if the blood had drained from them '. He proceeded on his way, but for the next 10 minutes he had considerable difficulty in keeping his feet on the foot-rests. Within an hour the legs felt normal. He attributed the loss of feeling in his legs to the mental shock which he experienced. Seven days later his legs felt tired and numb and he tended to drag the right one ". (McAlpine, 1946).

Onset.—C.P., aged 20, had a violent quarrel with his fiancée and broke off the engagement. In the middle of that night he was violently sick, and when he awoke in the morning the right arm and leg were useless.

Relapse.—J.W., aged 20, in 1940, during an air-raid, found she was unable to run to a shelter. When in the shelter she noticed tingling in her fingers and toes on flexing her neck.

Relapse.—C.F., aged 32, was restraining a hemiplegic patient when he had a further stroke. She walked quickly away for assistance, and almost immediately had a sensation of something bubbling down her spine ; her legs became stiff and weak, and remained so for four months.

Relapse.—E.M., aged 41, was unaffected by news of his mother's death from a stroke. Aged 42, on hearing of his father's death from a stroke, his walking became worse within a few hours, without improvement over the following three years.

Relapse.—H.B., aged 28 (during a progressive attack of weakness of the legs). Her little girl, who was pushing her doll's pram up and down the pavement outside the house, walked away and would not return when called. The patient became very anxious, but eventually her husband heard her cries and fetched the child. When the patient turned to go indoors she noticed a marked increase in the weakness of her legs, lasting for 10 days.

In these instances the association in time between the emotional stress and the onset or relapse of the disease is so striking that it is difficult to believe that it is purely coincidental.

It is necessary to approach the relationship between emotion and an attack of the disease from the opposite angle, and to examine the number of patients in whom a severe emotional stress at least once was not followed within a month by the onset or relapse of the disease. The relevant figures (Table V) show that such stress frequently is not followed by a bout of the disease.

Certain patients find that occasionally or invariably emotional disturbances, often of a specific kind, lead after a characteristic time-interval to an exacerbation of symptoms of a pre-existing lesion (Table VI). There is a significant difference ($\chi = 2{\cdot}8$) between the number of patients with disseminated sclerosis (18) and the number of

TABLE V

NUMBER OF PATIENTS WITH SEVERE EMOTIONAL STRESS NOT FOLLOWED WITHIN ONE MONTH BY ONSET OR RELAPSE OF THE DISEASE

Sex	Group	Number at Risk	Before Onset	After Onset
Male	D.S.	50	16	7
Male	Control	50	23	7
Female	D.S.	50	18	13
Female	Control	50	23	8

TABLE VI

EXACERBATION OF SYMPTOMS BY EMOTION

Sex	Group	Number at Risk	A. Invariably					B. Occasionally				
			Time Interval					Time Interval				
			Minute	Hour	Day	Week	Month	Minute	Hour	Day	Week	Month
Male ..	D.S.	50	10	—	—	—	—	6	—	—	—	—
Male ..	Control	47	2	1	—	—	1	—	—	1	—	—
Female ..	D.S.	50	8	3	1	—	—	1	3	2	—	—
Female ..	Control	50	3	3	1	—	—	2	—	2	—	—

controls (5) who state that a certain emotional stimulus leads invariably within the lapse of a minute to an exacerbation of symptoms. There is a tendency which does not reach the level of significance ($\chi = 1{\cdot}6$) for patients who describe themselves as " worriers " to suffer from these exacerbations ; there is no association, however, between the previous tendency for emotional stress to result in somatic symptoms and the exacerbation of a symptom of disseminated sclerosis by emotional stress. The following cases exhibited this exacerbation of symptoms.

Case 5.—Worry led to increase in unsteadiness.

Case 10.—Weakness of right hand and leg affected by any emotional stress—"anything not capable of a logical solution ".

Case 21.—Any form of anger led to increase of weakness of the left leg.

Case 23.—" Walking definitely worse when worrying about hospital or when self-conscious."

Case 27.—Anxiety led to tremor of the leg.

Case 28.—If really upset, sight and walking were affected within seconds.

Case 31.—Whenever frightened or quarrelling legs became weak for up to three hours.

Case 39.—" When I get nervy, numbness and weakness affect my right side."

Case 43.—Worries, especially self-consciousness, led to increase in weakness of the legs.

Case 45.—Blurring of vision became definitely worse when self-conscious, less so when worried, and was unaffected by anger.

Case 56.—" If pushed for time I get harassed, and my right leg is affected."

Case 57.—Emotional upset led to increase in numbness of the right leg lasting at times up to 24 hours.

Case 62.—Whenever " worked up " she got an immediate stiffening feeling in the legs ; she was able to do the same things, but had to make a greater effort.

Case 68.—On being insulted, picked up a chair to strike someone : " The chair had just reached the height of my shoulders when the strength left my arms and I dropped it. My legs were weak and I had to sit down."

Case 70.—Extract from a letter, June 1944 : " The present bombing is upsetting my nerves more than ever, and walking in consequence is dreadful. Immediately the alert sounds, so my legs stiffen."

Case 75.—When " strung-up ", legs affected for a minute or so.

Case 95.—Self-consciousness led to increase in double vision.

Case 96.—Emotion led to increase in unsteadiness.

Psychiatric Changes.—Various personality features of the patients before the onset of the disease were recorded above (Table III). The appearance or increase in these features after the onset of the disease are recorded in Table VII.

There is no significant difference in the trends shown by the patients with disseminated sclerosis and the control patients. In particular, hysteria was less frequent in the patients with disseminated sclerosis (twice) than in the control group (three times). Only four patients (three with disseminated sclerosis, one a control), noted a tendency for a feature to decrease or disappear. One of these patients was interviewed at the age of 50, 20 years after the onset of disseminated sclerosis. She gave a history of performing obsessional rituals since childhood. At the age of 45 she attended an unqualified lay " psychologist ", who gave her homely talks over a period of two years, during which time she lost her obsessional personality and neurosis. It is debatable whether this cure is to be ascribed to psychotherapy or to progressive organic disease of the brain. The relief of obsessional neurosis by prefrontal leucotomy suggests that a plaque of disseminated sclerosis interrupting fronto-thalamic tracts might result in a cure of this nature. A similar instance has been recorded by Braceland and Giffin (1950).

The patients in this series have been followed for too short a period to provide a reliable estimate of the incidence of psychosis in patients with disseminated sclerosis. A larger number of patients with disseminated sclerosis was therefore studied ; 544 patients last seen or traced in the years 1948 to 1950 had been followed for a total of 2,097 observation years. Of these patients, two were admitted to a mental hospital as certified patients :

TABLE VII

CHANGES, AFTER ONSET OF ILLNESS, IN FEATURES RECORDED IN TABLE III

Sex	Group	Number	1	2	3	4	5	6	7	8
Male	D.S.	50	2 (1)	—	3	—	—	—	—	4 (1)
	Control	50	3	1	2	1	—	—	—	2
Female	D.S.	50	1	2	1	2	1	—	—	1
	Control	50	2	2	—	—	1	—	—	4 (1)

Columns 1 to 8 as for Table III. Number of patients with feature appearing for first time. Additional numbers in brackets record patients in whom the feature, previously present, increased.

No. 77 of this series, a hysterical psychopath, was admitted to a mental hospital under certificate because of aggressive behaviour ; she was discharged however within a week.

L.T. Onset 33 ; aged 50 he became aurally and visually hallucinated, with delusions of persecution. He was admitted to a mental hospital under certificate because of occasional impulsive attacks.

The chances of a person in the third to sixth decades being admitted as a certified patient to a mental hospital in any one year for the first time is about 1 1,700 excluding patients, such as No. 77 above, discharged shortly after admission, (Slater, 1934–1935). The observed incidence amongst patients with disseminated sclerosis of admission to a mental hospital as a certified patient (1/2,097) is therefore lower than the incidence in the general population. No adequate figures for a control population are available to assess the incidence of psychosis not leading to certification.

Emotional Changes.—Specific inquiry (based on the questionnaire of Cottrell and Wilson, 1926) was made of each patient of changes since the onset of the illness in mood, in lability of affect, in control of emotional expression, and in bodily feeling. The number of patients who admitted to such changes, and the number of patients with impaired control over emotional expression which was not evident to themselves, are recorded in Table VIII.

The following significant differences were noted : an increase in cheerfulness of mood since the onset of the illness was noted by seven patients with disseminated sclerosis, and by no control patient (exact χ^2 gave $p = 0{\cdot}007$, a significant difference). A tendency to laugh more easily was admitted by six patients with disseminated sclerosis and by no control patient (exact χ^2 gave $p = 0{\cdot}014$, a significant difference). A tendency to laugh too easily, not admitted by the patient, was noted in 16 patients with disseminated sclerosis and in one control patient ($\chi = 3{\cdot}8$). A tendency to cry more easily was admitted by 29 patients with disseminated sclerosis and by 17 control patients ($\chi = 2{\cdot}0$).

The number (six) of patients with disseminated sclerosis who stated that after the onset of the disease they had an increase in bodily well-being at rest was greater than the number (two) of control patients, but the difference did not reach a significant level.

Intellectual Changes.—Three findings relevant to the assessment of intellectual impairment were noted (Table IX), namely a complaint of failing memory, a clinical impression of intellectual impairment, and a conceptual quotient below 70 (with a vocabulary score of 24 or above) on the Shipley (1940) Hartford Scale. The estimated incidence of impairment varied with each method of assessment from 15% to 28%. Of the three

TABLE VIII

EMOTIONAL CHANGES SINCE ONSET

Sex and Group		1	2	3	4	5	6	7	8	9	10	11	12	13	14	8+13
Male :	D.S. ..	20	3	—	2	12	1	1	5	—	15	3	16	6	1	11
	Control..	21	—	—	4	11	1	—	—	—	6	1	20	1	—	1
Female :	D.S. ..	25	4	2	6	15	1	—	1	2	14	3	23	10	—	11
	Control..	23	—	—	8	9	—	—	—	3	11	1	24	—	—	—

1. More depressed
2. More cheerful
3. More easily amused
4. Less easily amused
5. More easily depressed
6. Less easily depressed
7. Laughs less easily
8. Laughs more easily
9. Cries less easily
10. Cries more easily
11. Increase in bodily well-being
12. Decrease in bodily well-being
13. Objective observation, laughs too easily (not admitted by patient)
14. Objective observation, cries too easily (not admitted by patient)

TABLE IX

NUMBER OF PATIENTS WITH INTELLECTUAL IMPAIRMENT

Sex and Group		Complaint of Failing Memory. (Number at risk : 50)	Clinical Impression of Intellectual Impairment (No. at risk : 50)	C.Q. below 70 in those with Vocabulary Score of 24 or above on Shipley-Hartford Test	
					No. at Risk
Male :	D.S. ..	13	9	12	42
	Control ..	10	3	12	42
Female :	D.S. ..	10	6	13	46
	Control ..	11	3	11	47

methods of assessment, only the clinical impression of intellectual impairment was associated with a severe degree of physical disability, and this association did not quite reach the level of significance ($\chi = 1{\cdot}7$).

The association of the following emotional changes after the onset of the disease with intellectual impairment as estimated above was studied : increase in cheerfulness ; increase in bodily well-being ; increase in ease of laughter admitted by patient ; increase in ease of laughter not admitted by patient.

The following significant associations were found. Increase in ease of laughter not admitted by the patient was associated with a clinical impression of intellectual deterioration ($\chi = 2{\cdot}7$). Increase in ease of laughter, whether noted by the patient or the interviewer, was associated with a clinical impression of intellectual deterioration ($\chi = 3{\cdot}2$), and with a severe degree of neurological disability ($\chi = 2{\cdot}5$).

The clinical assessment of intellectual impairment depends in part on the appraisal of defects in judgment, as shown, for example, by the presence of undue or inappropriate laughter (Davies, 1949), and in the absence of a valid objective assessment of intellectual deterioration it cannot be concluded from these figures that the two features are necessarily interdependent.

A further investigation of intellectual impairment was made in an unselected series of 64 inpatients suffering from disseminated sclerosis, largely outside the present series (Appendix I). In addition seven female patients in a hospital for the chronic sick were tested ; these were selected as the most co-operative and least disabled in the hospital. Two tests were done by each patient, the Mill Hill vocabulary (synonyms, set B), and the progressive matrices 1938. The progressive matrices test is intended to assess " a person's present capacity for intellectual activity, whatever his education may be ", and the vocabulary test to assess " the fund of information he has acquired as a result of intellectual activity in the past " (Raven, 1950). Patients with intellectual impairment from organic disease of the brain tend to have relatively lower scores on the progressive matrices test than on the vocabulary scale. From the scores on the two tests each patient was placed in the centile appropriate to his score and age ; these were then expressed as average standard scores over the centiles 1 to 5, 6 to 25, 26 to 50, 51 to 75, 76 to 95, 96 to 100, in order to make the scores additive. From the difference of the standard scores of each patient the performance on each test could be compared. The mean difference between mild and moderate cases on the one hand, and severe cases on the other hand, of the difference between the average standard scores on each test was 0·809 (S.E. $\pm$ 0·359). There was therefore a significant difference in performance between mild and moderate cases on the one hand and severe cases on the other hand. The performance of severe cases was relatively impaired on the progressive matrices test, a finding which indicates intellectual impairment in that group.

Discussion

There are several causes for the discrepancies of opinion between authors who have investigated various psychiatric aspects of disseminated sclerosis. All psychiatric assessment has a large subjective variation. The diverse connotations given to certain terms (for example " euphoria ") make comparison difficult between any two series. The incidence of severity of neurological disability differs in various series, leading to variations in the frequency with which changes in personality following the illness are found. Finally in the frequent absence of any control series of patients the significance of the reported findings remains in doubt.

Premorbid Personality.—Most authors do not recognize a specific premorbid personality type in patients suffering from disseminated sclerosis. Those who find a hysterical personality appear to be dealing with a selected group, in that the patients described have submitted to prolonged psychotherapy or psychoanalysis. In this series hysterical manifestations before the onset of the disease were found less frequently in the patients with disseminated sclerosis than in the control series. The slightly higher incidence of a worrying temperament in the patients with disseminated sclerosis indicates that they do not regard themselves as " happy-go-lucky " (Grinker, Ham, and Robbins, 1950). In this series there was no difference in the distribution of the patients with disseminated sclerosis and the control series between the varieties of personality in the schemes chosen for classification (those of Jung and Sheldon), nor did any characteristic type of personality emerge from the group of patients with disseminated sclerosis. The use of the Thematic Apperception Test in a small group of patients did not suggest an undue incidence of suppressed aggression, which has been considered to play a part in the genesis of certain psychosomatic disorders.

Emotional Antecedents.—The factor of emotional stress in the genesis of the onset or relapse of disseminated sclerosis has been mentioned by many authors. However, those authors (Braceland and Giffin, 1950) who also studied a control series did

not consider that psychological trauma played a part, and Brickner and Simons (1950) noted that many patients were unaffected by emotional stress. In the present series, 38 patients with disseminated sclerosis and 26 of the control series admitted an emotional stress in the month preceding the onset of symptoms; the difference between the proportions, however, does not quite reach a level of significance ($\chi = 1{\cdot}8$). In most instances the emotional stress was not of undue degree or significance, and many patients appeared to be unaffected by similar or more severe stress. The number of instances (25%) of emotional disturbance antedating relapses in patients with disseminated sclerosis is very similar to that obtained (26%) for the onset of the disease in control patients. Nevertheless, even allowing for chance coincidence and the tendency for positive rather than negative associations to be reported, there are many striking instances of emotional stress antedating the onset or relapse of disseminated sclerosis. As Claude Bernard (1927) remarked on puncture diabetes: "negative facts when considered alone never teach us anything"; in a few instances emotional stress appears to have precipitated the onset or relapse of disseminated sclerosis. The finding of a significant tendency in patients with disseminated sclerosis for emotional stress to cause a transient exacerbation of symptoms due to a pre-existing lesion, possibly by way of a vascular mechanism, suggests that in certain patients (for example in the last case given above, "H.B.") short-lived disturbance of function may lead to a more lasting structural change.

Psychiatric Changes Following the Illness.—Estimates of the degree of anxiety in patients suffering from disseminated sclerosis differ widely (Ombredane, 1929; Harrower, 1950). In this series the number of patients with disseminated sclerosis who developed a worrying temperament did not suffer significantly from the number in the control series. Hysterical manifestations following the onset of the illness were less frequent in patients with disseminated sclerosis than in the control series. It is concluded that neither anxiety nor hysteria is a characteristic feature of patients with disseminated sclerosis. The disappearance of a long-standing obsessional neurosis in a patient with disseminated sclerosis suggests that a plaque of disseminated sclerosis interrupting fronto-thalamic tracts might produce an anatomical and functional change similar to that following pre-frontal leucotomy.

The incidence of disseminated sclerosis in patients of mental hospitals is no higher than in the general population (Howes, 1927). A follow-up investigation of a larger series of 544 patients with disseminated sclerosis revealed a lower incidence of certification than that expected in the general population of a similar age-group. However, two factors tend to lower the incidence of certification in patients with disseminated sclerosis. First, they may be unable from physical disability to commit actions leading to certification. Secondly a degree of dementia which in a physically fit person would require certification will probably in a patient with disseminated sclerosis be accompanied by a degree of physical disability determining admission to a hospital for the chronic sick rather than to a mental hospital.

Emotional Changes following the Illness.—Euphoria, defined in terms as discrepant as "cheerfulness" and "unconcern", has been accepted as a characteristic feature of disseminated sclerosis, in a widely varying percentage of patients. The discordant findings of Cottrell and Wilson (1926), and of Braceland and Giffin (1950) in a series containing many patients in common, have been mentioned above. In the present series an increase in cheerfulness since the onset of the disease was admitted by seven patients with disseminated sclerosis and by no control patient. Impaired control over the expression of laughter and of crying was found to be a significant feature of the patients with disseminated sclerosis; the former was associated with the clinical impression of intellectual impairment, and with a severe degree of neurological disability. An increase in eutonia since the onset of the disease was admitted by six patients with disseminated sclerosis and by two of the control series.

Intellectual Changes following the Illness.—Intellectual impairment was found by Canter (1951) in 23 patients on repeating an intelligence test (the American Army General Classification Test), initially given before the onset of the disease, after an average lapse of four years. He found impairment on the Wechsler-Bellevue test in 47 patients after the onset of the disease over as short a period as six months. Four indirect tests of intellectual impairment, depending on a discrepancy between performance on a vocabulary test and on a variety of other tests, also indicated the presence of intellectual impairment. In the present series intellectual impairment, variously assessed by a complaint of failing memory, by clinical judgment, and by the Shipley Hartford test, was present in from 15% to 28% of patients. In an additional investigation, 71 inpatients, largely outside the present series, were given two tests, the Mill Hill vocabulary synonyms set B, and the progressive

matrices, 1938. The performance of patients with a severe degree of neurological disability, as compared with those with mild and moderate degrees, was relatively impaired on the Progressive Matrices Test, indicating the presence of intellectual impairment in that group.

Summary

The findings in a selection of previous reports on various psychiatric aspects of disseminated sclerosis are reviewed. The causes of the discrepancies between these findings are considered.

An investigation was made of 100 patients with disseminated sclerosis and of 100 control patients attending a department for nervous diseases, with regard to premorbid personality, emotional antecedents of the illness, and psychiatric emotional and intellectual changes following the illness.

No specific premorbid personality type was defined in patients suffering from disseminated sclerosis.

Emotional stress antedating the onset or relapse of disseminated sclerosis was considered to be occasionally of significance.

A significant number of patients with disseminated sclerosis stated that an emotional stress, often of a specific nature, led invariably within the lapse of a minute to an exacerbation of symptoms due to a pre-existing lesion.

Anxiety, hysteria, and psychosis were found not to be features of disseminated sclerosis.

Emotional lability and intellectual impairment were found in a significant proportion of patients with disseminated sclerosis, especially in those with marked neurological disability.

My thanks are due to Dr. Douglas McAlpine, physician in charge of the department for nervous diseases, Middlesex Hospital, who was responsible for the initiation and guidance of this investigation. Professor L. S. Penrose gave invaluable advice on the treatment of the results of this study. To Dr. N. D. Compston and to Dr. W. A. Ll. Bowen I am indebted for many critical comments. Miss D. J. Kinloch Beck, Dr. Michael Kremer, and Dr. W. H. A. Pratt kindly allowed me to interview patients under their care. A part of this work was carried out during the tenure of a Comyns Berkeley Fellowship from The Middlesex Hospital Medical School.

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APPENDIX

TABLE I

DISTRIBUTION OF SCORES ON MILL HILL VOCABULARY AND PROGRESSIVE MATRICES TEST

Source	Sex	Degree of Disability	Number in Group	Test	Centile Group and Corresponding Average Standard Score					
					1–5 $-2{\cdot}062\sigma$	6–25 $-1{\cdot}073\sigma$	26–50 $-0{\cdot}324\sigma$	51–75 $+0{\cdot}324\sigma$	76–95 $+1{\cdot}073\sigma$	96–100 $+2{\cdot}062\sigma$
M.H.	M.	1 and 2	15	Mill Hill	—	—	4	4	4	3
M.H.	M.	3	7	Mill Hill	—	—	2	1	3	1
M.H.	M.	1 and 2	15	Progressive Matrices	—	—	1	1	8	5
M.H.	M.	3	7	Progressive Matrices	1	—	1	2	3	—
M.H.	F.	1 and 2	33	Mill Hill	—	3	9	6	8	7
M.H.	F.	3	9	Mill Hill	—	1	2	3	3	—
M.H.	F.	1 and 2	33	Progressive Matrices	—	1	4	7	12	9
M.H.	F.	3	9	Progressive Matrices	—	1	—	3	4	1
C.S.	F.	3	7	Mill Hill	—	2	1	2	2	—
C.S.*	F.	3	7	Progressive Matrices	4	1	1	—	1	—

C.S. = Hospital for Chronic Sick M.H. = Middlesex Hospital

TABLE II

SUM AND AVERAGE OF STANDARD SCORES

1	2	3	4	5	6	7	8
Source of Patients	Sex	Degree of Disability	Number in Group	Sum of Standard Scores on Mill Hill Vocabulary Test	5 / 4	Sum of Standard Scores on Progressive Matrices	7 / 4
Middlesex Hospital ..	M.	All	22	+15·435	+0·702	+20·275	+0·922
Middlesex Hospital ..	F.	All	42	+21·297	+0·507	+37·586	+0·895
Hospital for Chronic Sick	F.	Severe	7	+0·324	+0·046	−8·572	−1·224

TABLE III

COMPARISON OF DIFFERENCES BETWEEN AVERAGE STANDARD SCORES

Source of Patients	Sex	Degree of Disability	Number in Group	Sum of Standard Scores on Vocabulary Test Minus Sum of Scores on Progressive Matrices	5 / 4
Middlesex Hospital.. ..	M.	Mild and moderate	15	−8·416	−0·561
Middlesex Hospital.. ..	M.	Severe	7	+3·476	+0·496
Middlesex Hospital.. ..	F.	Mild and moderate	33	−12·506	−0·379
Middlesex Hospital.. ..	F.	Severe	9	−3·783	−0·420
Hospital for Chronic Sick ..	F.	Severe	7	+8·896	+1·271
All sources	M. and F.	Mild and moderate	48	−20·922	−0·436
All sources	M. and F.	Severe	23	+8·589	+0·373

Difference (column 6) between mild and moderate cases on the one hand and severe cases on the other = + 0·809.

$$SE = \pm\sqrt{\frac{2}{n_1}+\frac{2}{n_2}} = \pm 0{\cdot}359$$

BOOK REVIEWS

An Introduction to Modern Psychology. By O. L. Zangwill. 1950. New York : The Philosophical Library, Inc. 20 diagrams. Pp. 227. Price $3.75.

This little book will be read with interest by many. The author writes : " It is my belief . . . . that we may expect to witness the gradual evolution of a coherent science of mind within the broad framework of the biological sciences. It is this development . . . which . . . constitutes the modern trend ".

Following two chapters on experimental psychology, there follow some clearly expressed accounts of current knowledge regarding brain and mind, and other aspects of physiological psychology. He emphasizes the need for close collaboration between neurologist and psychologist, but warns psychologists of the danger of becoming merely ingenious technicians. Certainly there is no danger of this while the subject attracts scientists of Mr. Zangwill's ability, and he is to be congratulated on making this helpful contribution to understanding of what modern psychology is doing, and what it aims to achieve in the future.

Dementia Praecox or the Group of Schizophrenias. By Eugen Bleuler. Translated by Joseph Zinkin, with a Foreword by Nolan D. C. Lewis. 1951. London : George Allen and Unwin Ltd. Pp. xii + 548. Price 63*s*.

Bleuler's monograph is one of the great classics of psychiatry. Not long before his work was done, Kraepelin had introduced order into chaos in the clinical field by defining dementia praecox as a distinct syndrome, on the basis of careful study of the individual patient and follow-up through the years. The work of Freud was also new, and the interest in psychopathology had been awakened. Bleuler was one of the first to initiate the clinical analysis which separated and attempted to define the primary symptoms of the illness, common to all patients, from their secondary elaborations under the impress of personal factors. His work led him to the reformulation of the concept of dementia praecox into the more satisfactory concept of the schizophrenias, a formulation which is accepted today. We may doubt whether the attempt to find a single fundamental disturbance in the psychological field can ever be entirely successful in schizophrenia any more than in an organic psychosis such as Huntington's chorea. Nevertheless the attempt was a necessary one, and it brought a rich reward. The work of Bleuler, Jaspers, Gruhle, and others has brought clarity and comprehension into what was a welter of confusion ; and no clinician today attempts the differential diagnosis of schizophrenic from affective psychoses without proceeding along the lines which Bleuler outlined.

This book is a reminder of the unrecognized debt we owe to the past. Quite apart from the fact that it is the product of a mind of synthetic and analytic genius, the work shows a wealth of clinical observation and a painstaking attention to the form and meaning of the patient's symptoms which are usually beyond our reach today. Preoccupied with a rush to get the patient under treatment, or absorbed with the search for the psychogenetically intelligible, we seldom look at the patient with attentive and unbandaged eyes. It may be indeed that the clinical knowledge which should be part of the equipment of every student is in danger of being forgotten even by the teacher. The appearance of Bleuler's monograph in an English translation should do much to counteract this danger ; and it is to be hoped that it will be found on every library shelf and will be a compulsory text for examinations in psychiatry. The translator and the publishers have put us much in their debt.

Symbolic Realization. A New Method of Psychotherapy Applied to a Case of Schizophrenia. By M. A. Sechehaye. 1951. New York : International Universities Press, Inc. London : Bailey Bros. and Swinfen, Ltd. Pp. 184. Price 26*s*. ($3.25)

The author, a lay psychoanalyst, treated a schizophrenic girl first along orthodox analytic lines, and then by a method of her own devising. The patient had shown the first signs of mental abnormality about the age of 12, and was in an advanced hebephrenic state by the time she came to the analyst at 18. Treatment continued until she was 26, and had then practically recovered. She has remained well for 10 years since. The claim which is advanced for the new psychotherapeutic technique is based on this single remarkable case. The method itself consisted in attempting to understand the symbolic meaning of the patient's acts and utterances, and then answering her in the same symbolic language.

This work is the second in a series, *The Monograph Series on Schizophrenia*, of which the first was an English translation of Eugen Bleuler's classic monograph on the schizophrenias.

Die Moderne Psychiatrische Schockbehandlung. By Walter Ritter von Baeyer. 1951. Stuttgart : Georg Thieme. Pp. 161. Price DM. 14.70. ($3.45.)

Although the ground covered by this book is limited to insulin treatment, electric shock and treatment by chemical convulsants, and to the anoxic treatments, its quality is excellent. Indications, technique, and complications are discussed in detail ; and the practical part of the work is followed by clinically informed discussion of

the psychological and clinical results. Wide experience has helped the author to deal with the problem concerning the extent to which these treatments are specific to individual syndromes, and the extent to which they are symptomatic only. A final chapter is given to an attempt to explain their effect. The author proposes as his own view, which only explains part of the results observed, the idea that the release of a depression which may be brought about by a convulsion is caused by organically determined personality changes. The euphoria, the conative changes, the increased capacity for reacting to the environment, and the reduction in psychic productivity may all be included under this heading. Owing to a change in temperament, the patient is simply unable to have, or to complete, endogenously psychotic experiences, acts, and attitudes. This theory leaves too much unaccounted for, and is in conflict with too much, to be more than highly provisional. Nevertheless it is heuristically valuable because it poses new questions and leads to a search for observations of a new kind. The book is completed by a bibliography which includes all the more important contributions to what is now a very large literature.

Psychiatric Aspects of Juvenile Delinquency. By Lucien Bovet. 1951. Geneva : World Health Organization. Pp. 90. Price 5*s*.

This little booklet is the first number of a monograph series to be published by WHO. The author is attached to the Department of Justice of Vaud in Switzerland, and presumably has had considerable practical experience in the field of juvenile delinquency. His review is written with clarity and informed by sense. The discussion of sociological, constitutional, and other aspects of aetiology is balanced and critical ; but criticism gives place to a more enthusiastic attitude in the preservation of psychoanalytic views, and the author has been greatly influenced by Aichhorn. A large part of the book is given to the important preventive aspect. Although only about one juvenile delinquent in 10 becomes a recidivist, Dr. Bovet thinks that it is more important to provide a general psychiatric service for children than to concentrate on picking out the potential recidivist. The recommendations that are made, including the advice to young mothers, the provision that mothers should be constantly with their infants for the first three years, the multiplication of out-patient clinics for prevention rather than residential institutions for treatment, seem to depend on a doctrinaire rather than an empirical justification.

Zur forensischen Psychiatrie " geistig gesunder " Hirnbeschädigter. By Emil John, with a foreword by Professor Otto Pötzl. 1950. Vienna : Springer-Verlag. Two illustrations. Pp. 96. Price 13*s*.

The author takes as his text two murders committed by men who had suffered injuries to the brain. In the first case the prisoner had, in the course of a walking-tour in the mountains, when suffering from heat and exertion, hurled a stone at a woman unknown to him at the side of the path and killed her. He subsequently took some of her possessions from the corpse, but later discarded them. Investigation showed raised intracranial pressure and increased globulin in the C.S.F. as well as other indications of a chronic traumatic lesion. Juridically he was regarded as not responsible at the time of the act. In the second case a policeman of unblemished record engaged with an accomplice in stealing a pig. When challenged by a gendarme on the way home, and called on to give up his revolver, he shot the other twice in handing over the weapon. In this case physical findings showed little more than slight signs of a localized traumatic cerebral atrophy. The past history indicated an explosively psychopathic personality. The appeal court held that the emotions which caused the impulsive killing were themselves the result of a criminal procedure willingly and deliberately entered into, and that therefore he was to be regarded as accountable. From the discussion of these cases the author considers the forensic psychiatric aspects of head injury in general, the clinical methods which may be used in investigation, the lines along which clinical findings are relevant to legal decisions. In its special field, the contribution is a useful one, although in English law the existence of the M'Naghten rules make the legal position a very different one from that which is maintained in Austrian courts.

Studies in Lobotomy. Edited by Milton Greenblatt, Robert Arnot, and Harry C. Solomon. 1951. London : Wm. Heinemann Medical Books Ltd. 54 illustrations. Pp. 495. Price 63*s*.

This book is in many ways a contrast to that on leucotomy by Dr. Maurice Partridge recently published over here. Dr. Partridge approached the problem clinically, and reviewed all his cases personally. The present work is a symposium, and although the major part of it is headed " clinical considerations " as contrasted with " special studies ", in fact even the clinical aspect is approached by way of segregated studies such as " work adjustment ", " family adjustment ", " predicting the outcome " etc. It contains a large amount of factual information, probably more than there is in Partridge's book, but it does not give the dimensional picture of leucotomy as it presents to patients, their relatives and doctors, as does Partridge. Both methods of approach are necessary, but it may be argued that for a problem with such wide clinical and personal implications, Dr. Partridge's supplies more valuable insight. However, as far as special studies are concerned, the intensive circumscribed approach is more rewarding, though it may occasionally seem to make rather flimsy evidence appear substantial.

In a preliminary review of the literature, Greenblatt still apparently believes that leucotome cuts can be accurately assayed *in vivo*. This seems unduly optimistic. It is, however, encouraging to see that their standard operation is done by trephine and not burr-hole, which gives some added accuracy, and that a wedge of cortex from about area 9 is obtained for histology whenever possible.

The largest section of the book is a detailed one to four year follow-up of 205 cases. Here the study of

personality by fragmentation seems to have got rather out of hand. Thirty factors are considered ranging from " activity, amount of ", to " wetting " and " worry". The result does not seem to give more information than a properly conducted and recorded clinical examination, and in some respects gives a less complete picture. Thus " wetting ", " talkativeness ", and " restlessness ", which are capable of some objective assessment, are treated equally with such a subtle mental attribute as " orientation ", a feature which, it is becoming increasingly clear, is commonly, though not grossly, affected early after operation.

The authors claim that in both complete unilateral leucotomy and in bilateral cuts made only on the medial sides there may be therapeutic benefit. Physiologically, this might be expected, but the claim will need careful scrutiny.

One of the vexed questions in any leucotomy programme is whether formal rehabilitation and occupational therapy have any substantial effect on clinical results. The question is not answered here, though it is presumably recognized in the statement that " rehabilitation potentialities are very largely dependent on endogenous factors of growth ". Studies of the present type should lend themselves especially to giving an answer to such questions.

Amongst special studies the anatomical changes in six necropsy specimens are given, and attention is drawn to the large amount of connexions other than thalamic that the frontal areas possess, an orientation which will be welcome to many. The evidence for changed autonomic function after operation is also usefully reviewed.

In general the clinical sections of this work are disappointing. They appear to attempt a form of " scientific " accuracy unsuitable to the material. Measurement is not useful unless the units of measurement can be defined.

Psychosurgery. In the Treatment of Mental Disorders and Intractable Pain. By W. Freeman and J. W.Watts. 1950. Oxford : Blackwell Scientific Publications ; Springfield, Ill.: Charles Thomas. 2nd ed. 156 text figures. Pp. 574. Price 77*s*. 6*d*.

This is the second edition of a work which, when published in 1942, was the first comprehensive survey of frontal leucotomy. The book has been expanded and rearranged. The range of conditions for which therapeutic operations on the frontal lobe are undertaken has increased in the last 10 years. In general the indications remain psychiatric, but the method is no longer reserved for the most severe and otherwise hopeless psychotic cases. Certain disabling neuroses are more frequently treated ; and prolonged disabling painful states where the whole personality is being disorganized have recently been operated on in increasing numbers. Both these trends are illustrated in this new edition. The extension of neurosurgical treatment to cases of epilepsy with mental deficiency or other behaviour disorders is not considered. The attempt to find more limited effective operations is also somewhat briefly mentioned : the main emphasis is on the earlier standard (Freeman and Watts) cut and the authors' more radical leucotomy. The authors differ in their opinions about Freeman's transorbital leucotomy and each writes a separate section on this. Freeman's results on 400 cases certainly sound convincing, though most neurosurgeons will share Watts's hesitations about the blind passing of an instrument through the orbit into the brain (with the possibility of damage to paranasal sinuses) without full neurosurgical facilities to deal with complications that may arise.

Apart from the careful records of clinical results in a large number of cases, made more valuable by a 10-year follow-up in many instances and the histological study of necropsy material, the book contains a mass of interesting incidental observations of both psychological and physical changes following the operation. It is increasingly clear that the frontal lobes have subtle and important functions, and this book presents much valuable evidence for this. However, the authors wisely eschew dogmatic statements on the subject. It remains one of the most valuable reference works in this field, though its price in this country is a matter for dismay.

Spezielle Pathologie der Krankheiten des zentralen und peripheren Nervensystems. By Gerd Peters. 1951. Stuttgart : Georg Thieme. 214 illustrations. Pp. 437. Price DM. 56.–.

This textbook of special neuropathology is more comprehensive and informative than most of its kind in the English language, without aiming at the often tiresome completeness of a *Handbuch*. It also has the advantage of being very readable, as there are continuous references to the practical and clinical significance of the pathological findings. Interesting results of personal research are included, and problems, discussed lucidly and with a sense of sober criticism, are not evaded. The illustrations are instructive, carefully selected and excellently reproduced, and they strike a better balance between macroscopic and microscopic appearances than is found in many previous textbooks of neuropathology. Ample references guide the reader who wants fuller information, although it must be said that they are drawn predominantly from the literature in the German language.

The classification, although, as a whole, following traditional lines, has some unusual features, e.g. a chapter on brain lesions associated with primary disease of other organs and another on hypophyseo-hypothalamic syndromes. Psychiatric aspects of neuropathology are considered in several sections of the book. The author himself expects that his classification may occasionally arouse controversy. Some neurologists may be surprised to find the " inflammatory " type of demyelinizing disease (including disseminated sclerosis) separated from the " degenerative " leucoencephaloses and treated in different chapters. Swelling of the brain and oedema are still regarded as separate entities.

Neuropathology, in the German tradition perhaps even more than elsewhere, is still too exclusively the morbid anatomy of the nervous system, and this book is

no exception. Apart from the work of Hess, recent advances in neurophysiology, biochemistry, and related fields are not yet given their proper place. This is particularly evident in the discussion of the pathogenesis of extrapyramidal disease, vitamin deficiency, endocrine disorder, myasthenia gravis, epilepsy, and the functional psychoses. Even so, Professor Peters' book is valuable to the non-German reader as an important source of information on recent German work in neuropathology and, in particular, on the work of the school of Walter Spielmeyer to whose memory it is dedicated.

Medical Neuropathology. By I. M. Scheinker. 1951. Oxford : Blackwell Scientific Publications ; Springfield, Ill.: Charles Thomas. 186 text figures. Pp. 372. Price 75*s*.

This book concerns itself specially with the pathological changes in the nervous system associated with general medical disease. In chapters such as the one dealing with cerebral manifestations in cardiac disease and in lung disease, the C.N.S. findings are described in the setting of the general system of diseases. This will presumably add to its value for the general physician, but it gives a disjointed impression to the neurologist, whose clinical practice leads him to be quite as much interested in the physiological or biochemical aspect of the lesion as in its site. The book is well produced and the photomicrographs are adequate, but as a contribution to texts of medical neuropathology it has no special merit. Its price in this country seems fantastic.

The Transmission of Nerve Impulses at Neuroeffector Junctions and Peripheral Synapses. By Arturo Rosenblueth. 1950. Published jointly by The Technology Press of Massachusetts Institute of Technology and John Wiley & Sons, Inc. New York ; (London : Chapman and Hall, Ltd.) 98 text figures. Pp. 325. Price 48*s*. ($6.00.)

Neuroeffector junctions are defined by the author as " the junctions between the autonomic postganglionic nerve fibres with the heterogeneous effectors to which they distribute—smooth muscle, cardiac nodal tissue and cardiac muscle, and glands ". Peripheral synapses are described as junctions between two conducting elements with similar conducting properties, and in mammals this refers to autonomic ganglia and to the neuromuscular junctions of somatic muscles.

The book amplifies and extends the author's earlier work with the late Prof. W. B. Cannon, and draws freely on the author's later work. It is largely concerned with chemical transmission and emphasizes differences between the two types of junction. The neuroeffector type may be cholinergic or adrenergic with a further division of the latter into the sympathin E and I junctions. The peripheral synapses are considered to be solely cholinergic. The first part of the work deals mainly with the junctions of smooth muscle, and the case for purely chemical mediation in setting up the response in the effector is put forward. The second part deals with striated muscle, and chemical transmission is again considered to be all important. Acetyl choline is the essential transmitter, but it is further aided by potassium ions. The electrical theories of transmission are discussed, and while they are held to play very little part in the neuroeffector transmission, it is suggested that the spike potential of striated muscle has the function of determining the release of acetyl choline at the junction. Any more complete theories of electrical transmission are considered to be quite inadequate, but the author does conclude that further work is needed before the whole story is understood. Such work may indeed show a solution midway between the extreme chemical theory upheld here and the electrical theories.

The book is very well produced and illustrated. There are useful summaries to each chapter, and an extensive bibliography of over 700 references.

The Electrical Activity of the Nervous System. A Text-book for Students. By Mary A. B. Brazier. 1951. London : Sir Isaac Pitman & Sons Ltd. 96 illustrations. Pp. 220. Price 25*s*.

" This book is written for students with the purpose of bringing together under one cover a survey of the electrical activity of the nervous system." So writes the author, and she is to be congratulated on succeeding so well in this endeavour. Beginning with the peripheral nerve, she then considers the electrical activity of the spinal cord, special senses, and brain. Clearly written and well produced, this publication will be welcomed by those neurologists and psychologists who are not entirely up-to-date with their knowledge of electrophysiology. A well-chosen list of references follows each of the 18 chapters.

Emotions and Clinical Medicine. By S. Cobb, with an Introduction on Semantics and Definitions by J. R. Reid. 1950. London : Chapman and Hall. Pp. 243. Price 15*s*.

This book, despite its title, which suggests a layman's introduction to psychosomatic medicine, is likely to be of interest and value to neurologists, psychiatrists, and general physicians. Professor Cobb is one of the few practising neuropsychiatrists who is both competent and prepared to attempt a neurological correlation of psychiatric phenomena. That the correlation is still one of possibilities rather than certainties is one of the " necessities of the case ", as William James would put it. The present book takes its place as an extension and development of the author's previous works, especially his " Foundations of Neuropsychiatry " and " Borderlands of Psychiatry ". Their importance lies more, perhaps, in their point of view than in their factual content. The main bulk is based on the Salmon lectures for 1949, to which certain *pièces d'occasion* which are relevant to the main theme seem to have been added. This leads to a certain disjointedness in argument, though this is not unduly obtrusive. In the first chapters recent work on the anatomy and physiology of the neurological mechanisms for emotional appreciation and expression are reviewed. Next, the clinical impli-

cations of these facts are considered, and their application in the neuropsychiatric approach is illustrated by reference to anorexia nervosa.

The last few chapters are essays on various related themes. The question of specificity of psychogenic symptoms is discussed: the problem is not solved, but it is refreshing to see it raised again. Freud referred to it by implication in his early studies on hysteria; and Adler was concerned with it in his theories on "organ inferiority". It now obtrudes itself anew in a variety of "psychosomatic" conditions. As knowledge of neurological mechanisms underlying psychic states increases, it is likely to become of increasing interest. The "personality profile", as a guide to psychiatric diagnosis and prognosis, is also assessed with some much needed criticism.

The book is valuable because it appraises, rather than simply quotes, facts. It avoids dogmatism and has something of the "benevolent scepticism" which still recommends Bernard Hart's writings on psychopathology to a wide audience.

If neuropsychiatry is to become an integrated discipline it would seem that an attitude of mind must be developed in which psychiatric symptoms, small and great, are given their own value, and are considered as the correlates of brain changes, physiological, biochemical, and electrical, even though the exact relationship, the bridge between the two, may elude us. This book, with Professor Cobb's other cognate works, is at any rate the hope of a prolegomenon to such a discipline.

The Normal Encephalogram. By Leo M. Davidoff and Cornelius G. Dyke. 1951. London: Henry Kimpton. 3rd ed. 190 illustrations. Pp. 240. Price 42*s*.

This is the third edition of a book which has become widely known and valued for the clear and exhaustive description it contains of all aspects of the normal encephalogram. The various techniques of encephalography are reviewed, and there is a detailed consideration of the indications for the method and of the effects produced by intrathecal injection of different gases. However, the greater part of the book is concerned with the correlation of the radiological appearances with the anatomical structures outlined by the gas.

In describing the indications for encephalography, the authors recommend that it should be used in every case of organic brain disease in which there is doubt about the diagnosis, provided the intracranial pressure is not raised. This statement should now, perhaps, be slightly modified in view of recent developments in cerebral angiography to which encephalography may frequently be complementary. Not everyone will agree with the details of technique applied at the Neurological Institute at New York, but the descriptions given of many of the numerous methods used there and the excellent bibliography enable the merits of each to be compared.

The many illustrations are well reproduced and the points described can, with very few exceptions, be clearly seen. In a work which is so complete, it would, however, be an advantage if an addition was made to the standard views used by the authors, in order to include a postero-anterior half-axial projection in the erect posture. This would enable a further description of the appearances, in the antero-posterior plane, of the cisternae pontis and ambiens and of the fourth ventricle to be given, as distortions of these outlines are of importance in the diagnosis of lesions in the posterior fossa by means of encephalography.

This book is a valuable source of information for purposes of reference, and it provides a firm basis on which to build an evaluation of the abnormal. A companion volume on the abnormal pneumoencephalogram has recently been published.

Grundriss der traumatischen peripheren Nervenschädingungen. By G. Bodechtel, K. Krautzun, and F. Kazmeier. 1951. Stuttgart: Georg Thieme. 2nd ed. 78 illustrations. Pp. 106. Price DM. 10.20.

This short introduction to the study of nerve injuries is a disappointing publication. The approach to the subject is so elementary that many interesting and important aspects of the subject are completely ignored. However, the reviewer has recently been referring to the magnificent studies of nerve injuries by Foerster after the first world war, and this perhaps has led to his viewing this new publication with an unduly critical eye.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Le Syndrome de Morgagni-Morel. Étude Anatomo-Clinique. By André Calame, with a Foreword by E. Rutishauser. 1951. Paris: Masson & Cie. 27 text figures (including 13 plates). Pp. 154. Price Fr. Frs. 700·–.

Psychosurgery. In the Treatment of Mental Disorders and Intractable Pain. By Walter Freeman and James W. Watts. 1950. Oxford: Blackwell Scientific Publications; Springfield (Illinois): Charles Thomas. 2nd ed. 156 text figures. Pp. 574. Price 77*s*. 6*d*.

Analytic Group Psychotherapy. With Children, Adolescents, and Adults. By S. R. Slavson. 1950. Columbia University Press (London: Geoffrey Cumberlege). Pp. 261. Price 22*s*. 6*d*. net.

Speech Habilitation in Cerebral Palsy. By Marion T. Cass, with a Foreword by Winthrop Morgan Phelps. 1951. New York: Columbia University Press. Pp. 212. Price $3·00.

Die Nervenkrankheiten. By Georges Schaltenbrand. 1951. Stuttgart: Georg Thieme Verlag. 539 text figures. Pp. 880. Price DM. 87·–.

Atti del Convegno internazionale di Medicina del Lavoro. Editor: Clinica del Lavoro, Milan. Illustrated. Pp. 369 + 19. Price Lira 3,000 or $5·00.

Das Verstehen und Begreifen in der Psychiatrie. By F. A. Kehrer. 1951. Stuttgart : Georg Thieme Verlag. Pp. 58. Price DM. 5·70.

Bionome Psychotherapie. Ein grundsatzlicher Versuch. By J. H. Schultz. 1951. Stuttgart : Georg Thieme Verlag. Pp. 186. Price DM. 11·70.

Experiment in Dental Care. (Results of New Zealand's Use of School Dental Nurses.) By J. T. Fulton. 1951. Geneva : World Health Organization. 12 text figures. Pp. 87. Price Sw. Frs. 4. ($1·00).

Precepts and Counsels on Scientific Investigation. Stimulants of the Spirit. By S. Ramon y Cajal (edited and annotated by Cyril B. Courville). 1951. Mountain View (California) : Pacific Press Publishing Association. Pp. 180.

Studies of Undernutrition, Wuppertal 1946/49, S.R.S. 275. By Members of the Department of Experimental Medicine, Cambridge, and Associated Workers. 1951. London : His Majesty's Stationery Office. Illustrated. Pp. 404. Price 12*s.* 6*d.*

Brain Metabolism and Cerebral Disorders. By Harold E. Himwich. 1951. London : Baillière, Tindall & Cox ; Baltimore : The Williams and Wilkins Company. 52 text figures. Pp. 452. Price 46*s.* 6*d.* ($6·00).

The Unconscious Significance of Hair. By Charles Berg. 1951. London : George Allen & Unwin. Pp. 106. Price 15*s.*

Aspects of Form. A Symposium on Form in Nature and Art. Edited by Lancelot Law Whyte. London : Lund Humphries & Co. Ltd. Illustrated. Pp. 249. Price 21*s.*

The Postnatal Development of the Human Cerebral Cortex. Vol. IV. The Cortex of the Six-month Infant. By J. LeRoy Conel. 1951. Oxford University Press (London : Geoffrey Cumberlege) ; Cambridge (Mass.) : Harvard University Press. 233 text figures (with 108 plates). Pp. 189. Price 82*s.* 6*d.* ($12·50).

Diagnostic Encéphalographique. Encéphalogrammes normaux et pathologiques—Pathologie du liquide céphalique. By Pierre Duran. 1951. Paris : G. Doin & Cie. 26 text figures. Pp. 192. Price Fr. Frs. 1,100·–.

Les Hallucinations. Clinique et Physiopathologie. By Jean Lhermitte. 1951. Paris : G. Doin & Cie. Pp. 230. Price Fr. Frs. 930·–.

The Croonian Lectures on Muscular Movements and **Remarks on Paralysis of the Movements of the Trunk in Hemiplegia.** By the late Charles Beevor. London : Macmillan and Co. Ltd. Pp. 79. Price 5*s.*

INTERNATIONAL MEETING OF NEUROPATHOLOGISTS

The first international meeting of neuropathologists will be held in Rome from Monday, September 8, to Saturday, September 13, 1952. The President is Dr. Mario Gozzano (Rome), and the Secretary General, Dr. Armando Ferraro (New York).

Final arrangements are now being made for the programme. It has been decided that the following subjects should be discussed, one day being devoted to each subject : (1) histopathology of the demyelinating diseases ; (2) histopathology of vascular diseases ; (3) histopathology of schizophrenia ; (4) histopathology of mental deficiencies ; and (5) histopathology of senility.

Also part of one or more days will be devoted to short papers of special interest not related to the above subjects and to cinematographic and microscopical demonstrations.

The British Committee will be glad to receive offers of short papers for this meeting, especially of papers related to the five main topics. Those who wish to read papers should communicate with Dr. J. G. Greenfield at the National Hospital, Queen Square, London, W.C.1., or with any member of the British Committee, giving the full title of the paper and a summary showing in what respects it covers new ground.

British Committee : Dr. J. G. Greenfield, Hon. President.
Prof. Dorothy S. Russell, Vice-President.
Prof. J. H. Biggart.
Prof. A. Meyer.
Dr. W. Blackwood.
Dr. W. H. McMenemey.
Dr. R. M. Norman.

THE AUGUST (1951) ISSUE

The August (1951) issue contains the following papers :

The Surgical Treatment of Bleeding Intracranial Aneurysms. By Murray A. Falconer.

Sensory Disturbances in Cortical Wounds With Special Reference to Pain. By John Marshall.

Confirmation of the Rosenow Antibody-Antigen Skin Reaction in Idiopathic Epilepsy. By Edgar A. Bering, Jr.

Local Sign in Autonomic Responses. By Alick Elithorn, Malcolm F. Piercy, and Margaret A. Crosskey.

Subacute Necrotizing Encephalomyelopathy in an Infant. By Denis Leigh.

The Use of Marchi Staining in the Later Stages of Human Tract Degeneration. By Marion C. Smith.

Neuroticism and Emotional Instability in High-Grade Male Defectives. By N. O'Connor, M.A.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 7s. 6d.

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